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PRESIDENTIAL ADDRESS*

The Advance of American Medicine

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FIRST of all, I desire to thank you for the very great honor of acting as your presiding officer for a term which, by the fortunes of war, has been extended over a period of two years. No honors, I am sure, are more deeply appreciated than those bestowed by one's friends and professional associates. In these years, fraught with such perils to our countries and to our profession, I have faced the duties of this office in sincere humility, especially as I have recalled the fine men who have preceded me and the other wonderful Fellows of this association who have come and gone over the years.

World War II is passing into history. It is, therefore, fitting at this time that we express our gratitude and do honor to the members of our profession, especially to those of this organization who have served in the armed forces of Canada and of the United States. They have given of their time and of their lives to carry help to our sick and wounded. They have secured results such as have never before been obtained in time of war. We are very proud of these men and of the profession which has made the results of their work possible, not only by epoch-making discoveries in medical science, but also by the teaching, year after year, of the sound basic principles of medicine and surgery.

The growth of medical education and of medical practice in North America progressed very slowly in our scattered cities and communities during our pioneer days. Our first medical schools, hospitals, and medical libraries were not established until more than one hundred and fifty years after the founding

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of Jamestown. One must not, however, underestimate early American medicine, especially that of the period which began about 1750 and which characterized the remainder of the eighteenth century. Progress, during that time, was temporarily inhibited by the American Revolution but, following the war, it was definitely stimulated. Many courageous American physicians lived and worked during those pioneer years. They were men of outstanding personality, with good classical educations and with a knowledge of contemporary medical science gained in London, Edinburgh, Paris, Montpelier, and Leyden, the accepted centers of medical science and education of their day. Of these places Edinburgh seems to have been the most popular. The school was founded by Scotch pupils of Boerhaave (1668-1738) and it is said that the books and the principles of medical practice of that great Dutch clinical teacher and educational leader remained "dominant" in American medical practice until near the end of the eighteenth century. For many years, before and after the American Revolution, our predecessors, with the kindly help of some of the best clinicians in medical history, received their training in these centers during very important years in our medical progress. At home, these men passed on what they had learned to their associates by means of papers and courses of lectures and, through the old apprenticeship system functioning at its best, they helped to supply younger men with their knowledge of the basic sciences and with the much needed clinical training of the sick room. Most important of all they awakened in them an abiding desire for higher medical learning. It is well known that numerous prominent Americans, among them Benjamin Franklin, realizing the need of better medical education in the colonies and having an active desire to aid in its progress, were able, through their acquaintance and their influence abroad, to establish helpful medical contacts for our students and to aid greatly in their education.

It was in this way that we advanced at that period and that our medical schools were made possible. This craving for foreign study became so deeply ingrained in the traditions of our profession that only after World War I, with the decline of the European schools and the rapid improvement of our own, were our ambitious young men willing to complete their medical education at home. The average early American physician of this period, however, was unable to obtain the advantages of foreign study. His very limited preliminary schooling with his meager medical education was a poor preparation for practice. As a rule, however, he was an honest and practical counsellor, was a leader in his community, and was usually greatly loved as an individual.

The progress of American medicine in the early and middle decades of the nineteenth century and to the end of the Civil War in the United States was not outstanding. By this time our university medical schools and hospitals had been established and many independent schools had sprung up over the country, largely displacing the old apprenticeship system so important in the eighteenth century. The number of thoroughly educated physicians had greatly increased. Some of them, McDowell, Sims, Holmes, and many others had made conspicuous individual contributions to medical science. Advanced medical training, however, was still limited to a small proportion of our pro-

fession, and coordinated effort for scientific work was difficult in our scattered communities. Medical education in these years, while advancing slowly was, nevertheless, making very definite progress. The educated people of the time, however, and even our universities, seemed very slow to realize that good medical service throughout America was impossible without higher medical education at home. They did not yet fully comprehend that advancement in medical science is made, not through "theological dogma, metaphysical speculation," nor the pet theories of some forceful personality, but only through a vast amount of careful research in the physical, chemical, and biological sciences and in clinical medicine.

In 1870, Charles Eliot, a great educator and, at that time, the newly elected president of Harvard, found medical education in the United States still in a very primitive state of development. With few exceptions, there were extremely low entrance requirements and poor or almost nonexistent laboratories. Instruction was imparted by lectures from morning until night, and adequate clinical training was available for only a very few. There were many excellent teachers but their interest was blunted by the constant repetition of courses of lectures, often three times each year, to students poorly prepared to profit by their instruction. The final examinations were more or less nominal, and a degree of Doctor of Medicine, with the undisputed right to practice, could be secured after one year of study. At this low point in the progress of our profession, President Eliot made a significant statement: "The whole system of medical education in this country needs thorough reformation." Following this critical postwar period our schools improved more progressively, and the year 1870 marks the beginning of our modern era of medical education. From this date progress was also more rapid in the general field of education. According to studies at Harvard University in 1945, the population of the United States about tripled from 1870 to 1940, but in this same interval the enrollment in our high schools multiplied about ninety times and that in our colleges about thirty times.

In the second half of the nineteenth century, changes were taking place in Germany and in Central Europe which were to have a profound influence upon medical science and education in America. German medical science of the first decades of the nineteenth century was still greatly inhibited as the result of the Napoleonic Wars and by the racial and political disunity which existed among the German States and principalities. It was, however, in the fourth and fifth decades of that century that Johannes Müller (1801-58) and his many gifted pupils initiated the real era of scientific medicine in Germany. The rapid advancement, in that important period, was stimulated by the nationalistic spirit of the time arising from an intense desire for "racial and political solidarity." Progress, therefore, became very rapid in German medical science after the revolution of 1848, the consolidation of the German states into the German Empire in 1871, and following the establishment of peace in central Europe through the military and diplomatic efforts of Bismarck. Thereafter the center of advanced training and inspiration in scientific medicine shifted to Germany and to central Europe in about the last three decades of

the nineteenth century, and remained there until nearly 1914. Doctor William S. Halsted, who was greatly influenced by German surgery and was a student in that country at an early date, made some significant observations in his paper delivered as "The Annual Address in Medicine" at Yale University in 1904. He relates: "In the year 1876, the year when I first walked the wards of Bellevue Hospital, New York, the dawn of modern surgery in America had hardly begun." Again he states: "Thirty years ago as I sat upon the benches, often seven hours a day, listening to medical lectures, I was so impressed with the characters and lives of some of my teachers that I believed they represented all that was most advanced in medicine. But a day in Halle, at the clinic of Volkmann, was a revelation to me. There I heard by one of the young assistants at the early morning clinic an impromptu discourse on epithelioma at which I marvelled. At home the whole subject of tumors had been treated of in one lecture, in one hour, in the "tumor lecture." Again, he asks the question: "Why was Germany the country first to adopt antiseptic surgery? Why did almost every surgeon in every German University eagerly embrace Lister's system almost at the same moment and as soon as it was clearly presented? The answers to these questions are, I believe, to be sought mainly in the character of the scientific and practical training of surgeons in Germany."

Fortunately, by the last decade of the nineteenth century, well-organized and adequately endowed medical schools of a more modern type had been formed in some "five or six" of our universities. Anatomy, physiology, physiological chemistry, pharmacology, and pathology, with the rapidly growing subdivision of bacteriology, were no longer included in the general university curriculum, but had become integral departments of the medical school organizations under well-trained, full-time professors who were doing excellent research work. The clinical departments, likewise, were under the leadership of men of unusual training and ability. Most important of all, small groups of our best young men, attracted by these opportunities, were beginning a fine type of prolonged, personally supervised graduate training in an atmosphere conducive to higher medical learning. These young men and their pupils were later the professors and the teachers in the better type of medical school which made possible the rapid advancement in medical education of the last twenty-five years.

Unfortunately, such ideal conditions were not universally present. There were, as yet, not enough outstanding medical leaders and teachers in America with a true conception of the real meaning of advanced medical education, and there were entirely too few adequate endowments for medical schools of a modern type. The appearance, in 1910, of the Flexner report and the publication, in the same year, by our Council on Medical Education, of its first classification of medical schools and of its standards for an acceptable school, were followed by a revival of medical education in America which is still in progress. This upheaval in our educational system also brought to an end the era of the proprietary medical schools. They had long been fighting a losing battle against the rising cost of modern medical education and against the indifference of the public to the crying need of higher professional training in our

field. The development of the proprietary schools was, perhaps, a natural and a necessary part of the early growth of America, but they were no longer comparable to the modern medical departments developing in a few of our endowed universities. From the beginning, too, they were unfortunate in often being motivated by selfish aims and in lacking the support and the inspiration and leadership which they might have had as respected departments in our institutions of higher learning.

Such were the rather meager results of the first three hundred years of hard and discouraging effort for the establishment of medical education and of medical practice in the formative period of America. As pioneers, however, we had cleared our fields, good seed had been sown, and we were prepared to reap the harvest in the form of better medical education and better medical care in a century of greater opportunity.

America, at the turn of the twentieth century, was experiencing the culmination of a change in its social life, influencing every aspect of man's individual and cooperative effort. These changes come chiefly as the result of developments in our economic and industrial life which furnished both the stimulus and the financial support for many forms of social progress. We found ourselves changing from a nation which had been predominantly rural to one that was more largely urban and industrial. We perfected the principle of mass production in our factories. We developed various and extensive means of transportation and communication. We discovered large quantities of raw materials and, through research in physics and chemistry, we were able to employ more scientific methods in industry. We developed new means of generating power and new and more rapid ways of manufacturing commercial products and of making new and useful synthetic substances. Urbanization and the new and convenient means of transportation and communication brought the people of different parts of America together and broadened their outlook upon life. Large fortunes accumulated in the hands of charitable men, and libraries, universities, and hospitals benefited thereby. Large varieties of "desirable commodities and services" were created which stimulated commerce and added to human comfort and happiness. Thus in the first part of the twentieth century, and more especially in the last twenty-five years, the people of Canada and of the United States have made rapid progress and, fortunately, medical science has also advanced, but it has been profoundly stimulated and aided by the social and economic changes taking place.

The medical profession of 1946 also has many important problems, social, political, economic, and educational, all modified by the war and its ending. The educational needs of our returning medical veterans are many, and they are being efficiently met. The postwar reconversion of our medical schools is gradually being completed. It is reliably reported that all but five will return to their prewar calendar in 1946, and the remainder in 1947. Our schools, at the moment, are handicapped by the lack of adequately trained premedical students, by the scarcity of teachers for the preclinical branches, and of nurses for our teaching hospitals, and finally, by the still uncertain military status of

those desiring premedical education. The completion of the reconversion of our schools is made more urgent by the estimated postwar need of large numbers of doctors for the army, navy, and veterans' associations, and by the increased requirements of our civil population. With the end of the war serious financial problems are again arising in our medical schools due to diminishing government aid, lowered income from endowments, higher salaries to meet greater living costs, and enlarged pay rolls, as teachers return from the armed forces or from government service. Let us sincerely hope, if we are to have postwar military training, that it will be arranged to disrupt as little as possible the progress of our carefully planned peacetime medical education program.

Adequate premedical education is, as ever, a vital and much debated problem, and depends as much upon a wise choice of students of superior natural intelligence as upon their training. Unfortunately, it is in these important formative years that the medical student's education has been most often curtailed. The mere memorizing of large masses of facts and figures is not so important as that the student learn how to find and assemble them for himself, that he become able to grasp a problem quickly, think it through logically, and present his conclusion clearly to others. A university, moreover, has done little for a student which has not helped to formulate his conception of "right" and "wrong" from the "ethical" as well as from the "mathematical" point of view, and which has not called upon the natural enthusiasm of youth to develop his habits of work and his "latent initiative and talents," and which has not awakened in him an intense desire for knowledge and an ardent curiosity in every new step in his education. The physical, chemical, and biological sciences are intensely interesting and should never be allowed to appear dull or commonplace. This requires, however, individual and personal instruction, and is not easily accomplished by the more brutal methods of mass production in education. The premedical student will, of course, need the so-called general tools of education: the ability to read, write, and speak the English language correctly, fluently and understandingly and, with these, a working knowledge of at least one foreign language. He will need, moreover, some specific tools for his education, such as mathematics, physics, chemistry, and general biology, which will enable him to comprehend more quickly the basic principles of his lifework for medical science is, after all, in great part, a very complex form of mechanical and chemical engineering, but in a biological setting. Cultural training, too, is important, for he is to be a member of society as well as a physician. He should, therefore, have some knowledge of the history of mankind, of his literature, of his art, of his economic and social life, of his philosophies and religions, of his achievement, and of the things and ideals for which man, through the ages, has been willing to work, to fight, and to die. It has been said that such things take too much time and are not needed by a medical student. It will, however, give him at least some comprehension of the broad expanse of human knowledge and of man's thoughts and desires. It will also give him a more sympathetic understanding of his fellow men; it will create in him a desire to elevate the standards of his profession; and most important of all, will enable him personally to sustain a broad general view of life while

he must concentrate his energies upon the more narrow and more limited fields of medical science and practice.

The medical school curriculum has always changed from year to year to make room for new learning, but the modifications during the war have been chiefly adjustments to military necessity rather than permanent "advancements or improvements." The growing magnitude of the great mass of medical knowledge has required a constant search for methods by which a student may acquire a reasonable comprehensive but well-integrated and correlated course in the alloted time of four years. This has required careful interdepartmental cooperation in our schools with the elimination of much useless detail and a discriminating selection of that which should be taught. There is a growing tendency among professional medical educators to try out new methods. They would limit somewhat the teaching of the different branches of medical science as independent separate subjects, and would have the entire four years of the medical school curriculum made up of carefully integrated and correlated courses with the various phases of each course presented by teachers from different departments. Under this system fewer hours would be devoted to anatomy, physiology, and biochemistry as independent branches of science and more time to their study, as, correlated by nature in tissues, organs and physiologic fluids, they each play their part in the structure and the functioning of the body in health or in disease. Experimental physiology and experimental biochemistry with their many subdivisions, likewise, have become too complex and intricate to be extensively studied as independent sciences. The established knowledge, however, which workers in these fields have developed, is of great value and the student should know its significance and its limitations and should become familiar with its application in clinical diagnosis and treatment. Clinical instruction is being instituted earlier in the medical course and the time honored teaching of large classes by lectures is slowly giving way to the clinical clerkship system in which the student is a respected and active member of a small group responsible for the diagnosis and treatment of clinical cases. The relation of teacher and student is becoming more intimate, instruction is being imparted in smaller groups and visual methods of presentation are being used more and more.

Our intern service of one or two years supplements the clinical instruction of our medical schools and forms the foundation for general practice or, with certain modifications, for the medical and surgical specialties. It is well organized in our university hospitals but very much still needs to be done to develop the intern training program in our independent hospitals.

The modern conception of a graduate program for advanced training in the surgical specialties is less universally established than our intern system. It was making a small beginning in a few of our universities as early as 1900. In 1904, in his Yale address Halsted wrote: "Although we now have in the United States several (five or six) moderately well endowed medical schools with university connections, yet the problem of the education of our surgeons is still unsolved. Our present methods do not by any means suffice for their training." Much has been done for advanced graduate training in the surgi-

cal specialties since this was written forty-two years ago. Our schools are better endowed, facilities for training are greatly increased and are well organized. More and more well-trained men are coming along. Twenty-six thousand have passed their specialty boards in all branches of medicine, and yet the number of qualified men is still entirely inadequate to meet our growing needs. In Canada, as well as in the United States, this is true, especially in the smaller cities with their nearby rural communities, where a much larger percentage of the total amount of our major obstetrics, gynecology, and abdominal surgery than is generally realized is still in the care of inadequately trained men. Weir Mitchell had a saying which may emphasize the importance of this point. It runs as follows: "The rate of advancement in medicine is to be tested by what the country doctor is."

In the past, extensive changes in the fundamental ways of training our youth have been adopted very gradually. The war, however, has aroused an intense activity in the study of basic educational questions and of plans for the future development of our liberal arts colleges and universities. The educational literature has been actually flooded with articles and books upon these fundamental problems written by professional educators, by specially appointed committees from nearly all of our institutions of higher learning, and by members of organizations interested in this field of science. Plans are on foot in many of our colleges and universities to experiment with radical new ideas and to adopt drastic changes in their curriculums. We are already beginning to feel the impact of some of these revolutionary ideas in our medical schools.

Today we are living in an age of intense research activity. It is common practice in every phase of our social, professional, and industrial life. It has had a profoundly vitalizing influence upon our national life, and has been largely responsible for the social and industrial changes which have been taking place. Fundamental research, however, had its inception and was nourished in the laboratories of pure science in our universities, where generations of devoted men have labored for years on the basis of intellectual interest rather than personal gain. The profound and yet practical nature of the accomplishments of these men is, today, deeply impressed upon the minds of this generation through the spectacular and vital help which our universities were able to give to our war effort.

Modern medical research may be said to date from the year 1543 when Andreas Vesalius published his treatise, *De Fabrica Humani Corporis,* containing almost the first important advancements in anatomic knowledge since the death of Galen in A.D. 201. His work came at the end of the "dark ages" in medicine when authority had ruled supreme and men's minds had not been free to think and express themselves independently. The seventeenth century, which followed, was one of intense and brilliant anatomic research carried out by men whose names are familiar to us all in the pages of our books of anatomy. In this century the science of physiology had its birth and chemistry was not yet fully differentiated from alchemy. William Harvey, who was born in 1578 and active early in the seventeenth century, is generally considered

one of the most accomplished individual research workers in the whole history of experimental science. He was a great genius, not because, as an efficient technician and observer, he had many important isolated discoveries to his credit, but for the reason that he was a man of imagination, a deep thinker, and accustomed to meditate upon and to speculate about his scientific findings. It is known that his treatise, *De Motu Cordis et Sanguinis,* was not published until after at least nine years of thoughtful and laborious study and experimentation. His greatness was also in his intellectual ability to take a broad general view of a subject under investigation, to use simple, practical methods of proving the elements of his problems and, finally, to establish fundamental facts and guiding principles which, through the years, have been the basis for immense advancement in medical science. It was with this quality of mind that William Harvey was able to prove the circulation of the blood and to open to our consciousness that great highway which carries the essentials of life to every organ and to every cell in the body.

Modern medical education is inseparable from research activity. Through their union we have reaped a rich harvest of technological advancements in medical science and have created a sphere of endeavor where the principles of the basic sciences, of pathology and clinical medicine, and those of logic and common sense are brought together to solve the practical problems of medicine. The very spirit of research activity in our schools has stimulated the interest and the enthusiasm of both the teacher and the student in their everyday work, and has awakened their curiosity in the new facts and in the unsolved problems of medicine. They are no longer satisfied merely to "saturate" themselves with old established knowledge. It has also developed habits of precision, of careful direct observations, and of critical appraisal of collected evidence which are invaluable in medical practice as well as in the laboratory. Research has thus become an important and a vitalizing influence in medical education.

As a profession we are rather proud of the rapid advancements we have made in medical education and medical science in America. In the United States, however, we are somewhat alarmed by the powerful political and social pressure being brought upon us for radical changes in our methods of medical practice. It is necessary that we realize the importance of this situation. It is a problem of utmost concern to our people and to our profession. It is fundamental and should be settled only after most careful consideration. In the final analysis, no solution will be satisfactory to our people which does not follow the principles of our American way of life. We need, therefore, to face this situation honestly and intelligently, but we must be forceful enough and resourceful enough to maintain the position of leadership in the medical care of our people which the medical profession in a free country should occupy.

For years we have talked much about federalized medicine. It has been the opinion of the majority of our profession that governmental regimentation and political control of the practice of medicine would stifle initiative, would cause a deterioration in the quality of the services rendered the public, and

would interfere with the rapid, free, and unhampered progress which medical science and education have made in recent years.

As a profession, we have carried more than our share of the treatment of the indigent, but we have not always fully realized the plight of the very large low income group whose earnings cannot cover the cost of a major or prolonged illness. Therein lies much of the cause of the predicament in which we find ourselves today. These people are aware of the desirable and valuable services which modern medicine has made possible and they are anxious for a plan which will place these services within their reach. In this they are encouraged by organized labor, by a socially minded group in our federal government, and most of all by the medical profession. The only difference of opinion lies in the method by which these services are to be obtained. As a profession, we are not unlike an industry which has developed a desirable and much needed product but has given too little thought to a method of marketing it. We have lacked a sales department to devise a mutually satisfactory and workable plan by which this low income group could obtain adequate medical services under our American system of free enterprise.

Medical men, like other scientific groups, are naturally inarticulate on political matters. As long, however, as we choose to isolate ourselves from such things and remain politically impotent we must not complain if others, with less understanding and with less experience with medical problems, think and act for us. As in the early days of our Republic, the medical profession of today might make more effort to gain the respect and the confidence of Congress. As members of that body more of us might become good statesmen, and on occasion, shrewd but honest politicians. The protection of the health of a nation is one of the most important functions of Congress, but unfortunately, often the most neglected. We must, of course, strenuously oppose any form of arbitrarily or bureaucratically controlled medical practice. Nevertheless we must take a positive stand. We cannot forever remain merely a party of the opposition for, let us make no mistake, this rising demand of our people for fuller medical care is a challenge to our profession which will not be denied. No matter how this challenge is met, the undertaking is going to be a large one which can be accomplished only by closer cooperation between our government and our profession than exists today. With these two forces working honestly and wholeheartedly together, it will be possible to develop a workable plan, suitable to all concerned, which will not destroy the self-respect nor the freedom of action of our profession. Whatever the outcome of this controversy in the United States, however, and whatever effect it may have upon us personally, we should remember that it is our sacred and sworn duty to work unselfishly for the best interests of the American people. If we do not do this we shall deserve to lose the confidence and the respect of the public which we have gained through many generations of hard, unselfish work.

With your indulgence, may we discuss some matters relative to our own association? Since the beginning of the war we have missed two of our annual meetings and three of our midyear meetings. While poetically, Thomas Haynes Bayley (1797-1839), an early English song writer and author, may

have been correct when he wrote in his poem *The Isle of Beauty:* "Absence makes the heart grow fonder," yet practically in medical organizations, interest thrives upon frequent meetings, excellent programs, and good fellowship. It would seem appropriate, therefore, as we gather in this immediate postwar period, after so many interruptions in our professional life, that we should pledge renewed support to every phase of our organized effort and give careful consideration to ways and means of improving our association and of making it as effective and influential as possible.

In 1888, when this association was founded, the population of Canada and of the United States was smaller than at present. Today, not only is the population of our two countries larger, but, with better and more extensive educational facilities, the number of men more thoroughly trained in our specialty has become relatively greater. Should we not, therefore, along with other organizations in our specialty, give careful consideration to deserving members of this group and, as they gain experience and show their worth, make room for them in larger numbers in our obstetric and gynecologic organizations? For some years the membership of our association has averaged about one hundred and thirty and, with the addition of four or five new men each year, it has remained nearly stationary. This has made our meetings very companionable and our fees have about met our expenses. Would this, nevertheless, not be an opportune time to increase our membership more nearly to our constitutional limit of one hundred and fifty Fellows? More room might be made for new members and our ranks closed for more active participation in our programs, by enforcing more strictly paragraph XI of our by-laws relating to attendance. The scope of our future programs, moreover, might be broadened if new men were selected with as diversified special interests as possible within the bounds of obstetrics, gynecology, and related surgery and also if the number of men in our whole association, primarily interested in one or the other of the two major divisions of our specialty, were fairly evenly divided.

The scientic programs of any medical organization are, of course, necessary to its success. If these programs are not of enough volume nor sufficiently diversified to meet the special interests of each member, some will tend to lose interest and drift away. For some years the programs of this association have consisted of about nineteen papers. Four of these are usually presented by invited guests. One is the Foundation Prize Thesis, and one the president's address As a rule one or two of the papers on the program are not presented because the members are unable to attend the meeting. The remaining eleven or twelve scientific papers thus presented by our Fellows do not seem a very large volume of work for an organization of one hundred and thirty members. Some years ago many more papers were presented, as our older transactions show. This was accomplished, however, by holding long morning, afternoon. and evening sessions. It was a tiring experience and gave little time for recreation or for members to become acquainted. Would not, however, some method of increasing the volume of our work be of value to our Association? Could this be accomplished, during the three days of our meeting, by classifying our

papers and holding a few separate simultaneous sessions, one for papers purely obstetric and the other for those devoted entirely to gynecology and related surgery? Papers of interest to both groups could be presented by joint session as at present. This would make possible a larger and more diversified program to suit the special interests of each member, would increase the size and importance of our transactions, and would better repay us for the not inconsiderable expenditure of time and money incurred in attending our meetings.

In the constitution of our association it is stated: "Its object shall be the cultivation and promotion of knowledge in whatever relates to obstetrics, gynecology, and abdominal surgery, except that which is peculiar to the male." In recent years, as the specialties have become more sharply defined, this has, by common consent, been interpreted, if one can express the unwritten law accurately, to include only such abdominal surgery as is closely and necessarily related to obstetrics or gynecology. In this we have followed the trend of the times. It may be rightly said that obstetrics is probably the oldest specialty and, combined with gynecology and related abdominal surgery, one of the largest, also that there is thus formed a natural specialty, limited to one sex and circumscribed by a common anatomy, a common physiology, and a common pathology. Our specialty, moreover, has amply justified its existence by striking advancements in medical science and by gratifying improvement in clinical practice.

Are the specialties, however, as they exist in American medicine today, entirely independent of one another? Is any one of them a thing apart in medical science? Are they not all very closely related to each other and to the basic sciences and to the principles governing medicine and surgery? Our specialties are major divisions of medical science and each has many spheres of activity where knowledge of much value to other specialties is available. In the most orthodox practice of a specialty, we must often cross the strictly defined boundaries of other divisions of medicine or surgery. Is there not, therefore, an undesirable influence in what some are pleased to call overspecialization, with too sharp an interpretation of the lines between the specialties and too narrow a view of what each should include? Is it not one of the pitfalls of specialism to concentrate unduly upon limited fields in clinical medicine and to lose the stimulus and the broadening influence of contacts with other divisions of medicine? Is it wise to lose touch with the general body of medical knowledge and should we not hold fast to its guiding principles? It is, of course, true that, as medical knowledge within our specialties has become more complex, we have each individually been obliged to accept a more limited field of endeavor. The workers within a specialty, however, comprise a whole group of men with widely varying activities within the separate departments of their specialty. The combined interests of such a group are much broader than those of an individual and will be found to cover not only every phase of their specialty but also all knowledge related to it.

The application of these thoughts to our own association would seem to be, that we should have as broad a general policy as possible within the bounds of our constitution as now interpreted. It would also mean that we should

adapt our scientific programs to meet the needs of workers in every phase of our specialty and be willing to include in these programs not only subjects of interest in every phase of obstetrics, gynecology, and related surgery, but also those subjects of special interest and value to our members which may arise in any field of medical science. This is not an argument against specialism but a plea for a broader conception of this extremely valuable trend in modern medicine.

World War I and, especially, World War II have caused a serious interruption or the utter destruction of the progress of medical science and education in many parts of Europe and Asia and in the world at large. It becomes the responsibility, therefore, of those of us living in areas less seriously affected to bear the torch of medical progress for the rest of the world. The burden of this responsibility will fall heavily upon the people of the British Commonwealth and upon the citizens of the United States. If, through lack of aggressive, intelligent, and cooperative effort or because of unwise leadership or the blight of bureaucratic control, we allow this torch to fall, the light of medical science will quickly fail and the people of the world will suffer a loss which will not be replaced for many generations. Is it not the responsibility, therefore, not only of our universities and of our medical schools but also of such educational groups as our own, to do all in our power to improve our organized efforts for the advancement of medical education and of medical science and practice? Is it not also our duty, as living members of our own revered association, to maintain the broad-minded, high standard of excellence set for us by the Founders of this Association and sustained for so many years by the fine Fellows who followed them?

PREGNANCY IN THE PATIENT WITH HYPERTENSIVE DISEASE*

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JERSEY CITY, N. J.

(From the Margaret Hague Maternity Hospital)

WE HAVE thought it worth while to survey our experience with pregnancy in women with hypertensive disease. There are relatively few such studies based upon any considerable series, and in most studies extant there has been a selective factor in that therapeutic abortion has been done in the more severely hypertensive patients. It has not been our policy to abort such women, and our large material therefore offers an almost unique opportunity for the study of the natural history of pregnancy in hypertensive women.

Material and Methods

We have selected from our toxemia files all women in whom recorded blood pressures before the twenty-fourth week of gestation permit the diagnosis of "hypertensive toxemia." In the thirteen-year period from the opening of the hospital in October, 1931, through 1944, there were 301 pregnancies occurring in 218 women, in whom the diagnosis of hypertensive disease could be established by this criterion. We have taken only those cases where (a) hypertension was known to have existed before pregnancy, or (b) hypertension was found before the twenty-fourth week of gestation, no previous normal readings having been recorded. Our standard for hypertension is 140/90 or greater. Patients showing hypertensive levels of blood pressure only at the initial clinic visit were excluded. Recognizable cases of glomerulonephritis and pyelonephritis were rejected; however, 15 patients (7 per cent of the series) were classifiable as "renal disease." We believe that these were either cases of nephrosclerosis secondary to hypertensive disease, or cases with superimposed pre-eclampsia.

Our postpartum toxemia clinic records have been of great value, in that they have given us repeated blood pressure readings while the patients were not pregnant. Also, we have looked through the record room files of every hospital in Hudson County, and whenever we found an admission of one of our patients—before or after she came into our hands—we have studied the hospital chart.

Renal function was assessed by Fishberg's simple urine concentration test,[4] and by the urea clearance. Blood and urine ureas were determined by Van Slyke's manometric urease methods.[6] Urinary protein was estimated by the sulfosalicylic acid method, and quantitative measurements were made by the procedure of McKay (Peters and Van Slyke[6]).

The Patients

There were 194 white and 24 Negro patients, a ratio of 8:1. In all hospital admissions, the ratio is 18:1. At the time of the pregnancy in which the original diagnosis of hypertensive disease was made, they ranged in age from 16 to 44, with half in their thirties; the average age was 32½ years. Nearly one-fourth (66) were para 0, although 16 of these had had previous abortions; eight were elderly primiparas. Half of the patients were para iii or greater.

*Presented, by invitation, at the Fifty-Seventh Annual Meeting of the American Association of Obstetricians, Gynecologists, and Abdominal Surgeons, Hot Springs, Va., Sept. 5 to 7, 1946.

There had been 840 gestations prior to the pregnancy in which the diagnosis of hypertensive disease was definitely made. The uncorrected fetal loss in these earlier pregnancies was 292, or 34.8 per cent. This checks almost exactly with the data of Browne and Dodds.[1] Seventy-six per cent of the multigravidas gave a history of previous toxic pregnancy. The history was unknown in 23 per cent, and in only two cases were the previous pregnancies known to be normal.

The medical history, as given by the patients, revealed scarlet fever in 10 per cent, rheumatic fever in 9 per cent, diabetes in 1 per cent, pyelitis in 1 per cent, and hypertension antedating pregnancy in 60 per cent.

The family history, which we do not regard as reliable, was said to be positive for "heart trouble," "kidney trouble," "strokes," or diabetes in 66 per cent. Sixteen patients (7.3 per cent) had had mothers or sisters dying in childbirth.

Fifty of the patients had 47 sisters and 15 daughters who delivered here in 112 pregnancies. Toxemia, often "pure" pre-eclampsia, occurred in 34 (30.4 per cent) of these pregnancies. This is five times the incidence of toxemia in our hospital. The 47 sisters delivered 92 babies, with a toxemia incidence of 35.9 per cent. Of the sisters, 44.7 per cent had at least one toxic pregnancy. Only one daughter had a toxemia.

The Pregnancies

Blood Pressure.—The height of the systolic blood pressure, either before pregnancy, or as found early in pregnancy, is shown in the first five lines of Table I. Where the initial blood pressure is recorded after the twenty-fourth week, the chart shows a physician's statement to the effect that hypertension had been found earlier.

The blood pressure often drops markedly in midpregnancy, as has been reported by Reid and Teel,[7] and others. There were 106 pregnancies, with sufficient data to compare repeated prepregnant or first trimester pressures with pressures observed in the second trimester. A decrease of more than 20 mm. Hg. was found in 39.6 per cent; the blood pressure drop exceeded 40 mm. in 11.3 per cent. No change (i.e., less than 20 mm. Hg.) was found in 50 per cent, and an increase of more than 20 mm. was seen in 10.4 per cent (see Table I, line 6).

Often the pressure rose again toward the end of pregnancy. We have comparative data for 163 pregnancies. In 52.7 per cent, there was not a significant change from the second trimester readings. There was an increase of more than 20 mm. in 44.2 per cent, and in 16.6 per cent this rise exceeded 40 mm. Only five patients (3.1 per cent) showed a blood pressure decrease in the last trimester. The distribution of blood pressures near term is shown in Table II.

Usually the patients whose blood pressures rose in the last trimester were the ones whose pressures had dropped in midpregnancy. Superimposed preeclampsia or eclampsia occurred in some patients, thus accounting for some of the late increases.

The data in Table I, lines 7, 8, and 9, indicate that in nearly half (49 per cent) of the patients the systolic blood pressure near delivery was about the same as before pregnancy or early in pregnancy. In 21 per cent it was lower, and in 30 per cent, higher. The higher the initial pressure, the larger is the proportion of patients showing drops in pressure. Also, the lower the original pressure, the larger is the proportion of patients who have marked rises near delivery. The diastolic pressures showed the same trends as the systolic.

Case 1.—As an extreme and interesting example of the blood pressure reduction often seen in pregnancy, we cite the case of M. R., History No. 25403. Her first pregnancy, in 1934 and at another hospital, was complicated by an unclassified toxemia. We first saw her Jan. 30, 1936, in about the thirty-fourth

TABLE I. SUMMARY OF PREGNANCY AND FOLLOW-UP FINDINGS IN 218 HYPERTENSIVE WOMEN HAVING 301 PREGNANCIES AT THE MARGARET HAGUE MATERNITY HOSPITAL

INITIAL SYSTOLIC BLOOD PRESSURE, MM. HG.:	140 TO 159	160 TO 179	180 TO 199	200 OR MORE	TOTALS
Based upon pregnancies					
Total pregnancies	123	92	43	43	301
First recorded blood pressure					
Prepregnant, cases:	28	32	16	15	91
First trimester, cases:	24	22	7	5	58
Second trimester, cases:	65	25	13	16	119
Third trimester, cases:	6	13	7	7	33
Proportion with midpregnancy drop in blood pressure (106 cases), per cent:	28.9	48.4	56.3	42.9	39.6
Blood pressure near delivery, compared with initial recording					
Lower, per cent:	1.8	31.5	36.8	40.5	20.8
Same (±20 mm. Hg.) per cent:	55.8	43.8	39.5	48.7	49.1
Higher, per cent:	42.4	24.7	23.7	10.8	30.1
Incidence of superimposed toxemia in 149 cases with prepregnant or first trimester blood pressure recordings, per cent:	28.9	27.8	30.4	30.0	28.8
Fetal mortality, per cent:	31.7	32.6	39.5	67.4	38.2

TABLE II. PROTEINURIA IN RELATION TO DEGREE OF HYPERTENSION (NEAR DELIVERY) IN 300 HYPERTENSIVE PREGNANCIES

SYSTOLIC BLOOD PRESSURE, MM. HG.:	140 TO 179	180 TO 199	200 TO 219	220 OR MORE	TOTALS
Total cases	187	64	33	16	300
Urine normal, per cent	66.8	36.0	12.1	0	50.7
Possibly significant proteinuria (''trace''), per cent	11.8	10.9	18.2	6.3	12.0
Significant proteinuria, per cent	21.4	53.1	69.7	93.7	37.3

week of pregnancy. She was a Negro woman 32 years of age, gravida ii, para i, estimated date of confinement, March 14, 1936. She weighed 177 pounds, with a gain of 21 pounds over the prepregnancy weight. Blood pressure 140/90, no proteinuria, no edema, and no complaints. One week later, she came in, in active labor, and delivered a living baby. The blood pressure in labor was 140/95, and was no higher during her hospital stay. On March 20, six weeks postpartum, the pressure was 190/120. She was seen many times subsequently, and the lowest nonpregnant pressure ever observed was 180/105.

We saw her in four later pregnancies, and frequently between all pregnancies. The nonpregnant blood pressures ranged from 180/105 to 280/160. In every pregnancy, except the fifth, which aborted at three months, the blood pressure dropped to low normal levels, and usually rose to 140-150/90-98 in the last month. All pregnancies but the fifth and sixth eventuated in live births. Within two weeks post partum, the blood pressure rose markedly after every pregnancy, and was never below 180/105. In February, 1940, she was admitted to the hospital for a workup, at which time she was ten months post partum. In eight days of bed rest, her pressure varied from 224/140 to 280/160. She had frequent severe headaches, vomiting, blurring of vision, and cardiac enlargement and insufficiency (generalized edema and dyspnea). The retinal arteries were tortuous and beaded.

In October, 1940, she again became pregnant for the sixth time, and had a cerebral accident at about the time of conception. We first saw her again when she was six months pregnant. Weekly blood pressure readings varied from 110/60 to 130/80, except for one of 170/120 obtained when hospitalization was

suggested. At the thirty-seventh week, the pressure rose to 150/98, and then in succeeding weeks fell to 140/86. She never had any edema, proteinuria, or complaints. At forty-one weeks (July 6, 1941), she came in, in active labor and in good spirits. While in the admitting room, she suddenly had a tonic convulsion and died within ten minutes. The urine obtained in the admitting room showed a two plus proteinuria. Blood pressure was unobtainable (shock). Autopsy showed a cervical tear extending up the wall of the uterus to the tube and ovary (she had never had a cesarean section). Other findings were: marked cardiac hypertrophy, nephrosclerosis, an old right capsular cerebral thrombosis, and the liver changes of eclampsia.

Renal function tests, repeated many times, were always normal. Two months before death, the urinary specific gravity was 1.026 and the urea clearance 108 per cent. Except for the last urine, she never showed more than a very faint trace of proteinuria in the five years of close observation.

Proteinuria.—In half of the 301 pregnancies, the patients never had more than a very faint trace of proteinuria. The other half showed pathologic amounts in varying amounts, but only as they approached term. Proteinuria was definitely related to the greater degrees of hypertension (Table II), as has been found by others. Of the 65 patients who had a proteinuria of 8 Gm. per liter or more, 78.4 per cent had systolic pressures above 180 mm. Hg.

Renal Function.—Tests of renal function were made in all but eight pregnancies. In the simple Fishberg test, the patients in 58.5 per cent of the pregnancies had urinary specific gravities of 1.022 or higher and, an additional 18 per cent concentrated to 1.019 to 1.021. Since nearly all patients were on a restricted salt intake, and often on a low protein diet as well, we believe that three-fourths of the patients thereby proved normal renal function. (See Chesley[2] for discussion of renal function tests during pregnancy.) Urea clearances were done in 194 patients, including all who failed to concentrate to 1.022. Urea clearances of less than 50 per cent were found in eight patients, 50 to 59 per cent in seven, and 60 to 69 in fourteen. If we accept 60 per cent as the lower limit of normal, then 15 patients, or 7 per cent of the series, had renal impairment.

Superimposed Toxemia.—Nine pregnancies, in eight patients, were eclamptic. As for pre-eclampsia, we find it difficult to decide in many cases whether or not to make the diagnosis. As mentioned above, nearly half of the patients in the last trimester show rises of more than 20 mm. Hg over the blood pressure level of midpregnancy, and half showed some degree of proteinuria. If, however, we require both a rise in blood pressure and proteinuria, or marked proteinuria alone, then only 81 pregnancies could be considered as pre-eclamptic. By this criterion (perhaps too strict), the incidence of superimposed pre-eclampsia and eclampsia would be 29.9 per cent, or in pregnancies carrying past the twenty-fourth week, 34 per cent. This figure is considerably below those of Reid and Teel[7] (63 to 70 per cent), Wellen[8] (86 per cent), Dexter and Weiss[3] (50 per cent), or Mussey, Hunt, and Sluder[5] (51 per cent), but higher than the 17.9 per cent of Browne and Dodds.[1] These last writers, however, found that 82 per cent of their patients showed some "exacerbation" of the disease, i.e., increased blood pressure, or proteinuria, or edema, or other signs and symptoms of toxemia. The estimated incidence of toxemia depends, of course, upon the diagnostic criteria.

Premature separation of the placenta occurred in 17 cases, or 5.6 per cent. Nine of these were associated with superimposed toxemia, giving an incidence of ten per cent in the toxemic pregnancies.

Since the superimposition of toxemia is of crucial importance, as will be shown later, we have sought for some indication as to which women might be more susceptible.

There is no relation between the incidence of superimposed toxemia and the prepregnant or first-trimester level of blood pressure (Table I, line 10). Nor, as Table III shows, is there any clear-cut correlation with the parity of the patient, although toxemia is somewhat more prevalent in primiparas. The incidence in para iv, v, and vi patients is about half that in the others. The age relation is about the same as that of the parity, as might be expected (Table IV). Superimposed toxemia is somewhat more common in the younger hypertensives.

TABLE III. THE SUPERIMPOSITION OF TOXEMIA IN RELATION TO THE PARITY OF HYPERTENSIVE PATIENTS CARRYING PAST THE TWENTY-FOURTH WEEK

PARA:	0	I	II	III	IV	V	VI	VII OR MORE	TOTALS
Total cases	57	51	39	25	23	14	13	41	263
Superimposed toxemia, cases	26	19	12	8	4	3	3	15	90
Toxemia incidence, per cent	46	37	31	32	17	21	23	37	34

TABLE IV. THE SUPERIMPOSITION OF TOXEMIA IN RELATION TO THE AGE OF HYPERTENSIVE PATIENTS CARRYING PAST THE TWENTY-FOURTH WEEK

AGE, YEARS:	LESS THAN 25	26 TO 30	31 TO 35	36 TO 40	41 TO 45
Total cases	38	63	74	60	28
Superimposed toxemia, cases	18	23	19	22	8
Toxemia incidence, per cent	47	36	26	37	29

Nineteen of the hypertensive patients who also had eclampsia or preeclampsia have had pregnancies subsequent to the one in which the diagnosis of hypertensive disease with superimposed toxemia was made. Ten, or 53 per cent, of these later pregnancies were again toxic. However, three women aborted and two delivered at home. Excluding these, the incidence of recurrent toxemia would be 71 per cent.

Hypertensive patients *not* showing superimposed toxemia in one or more pregnancies *may* show it in subsequent ones. Thus, in 63 subsequent pregnancies observed in women initially escaping toxemia, 16 cases, or 25.4 per cent, were toxic. This incidence approaches the total incidence of 34 per cent for the whole series.

The Labors

In the 301 pregnancies, two patients died before delivery. Thirty-four were sectioned, 28 before the onset of labor. In the remaining 265 cases (including abortions), onset of labor was spontaneous in 181 (including six who came to section), or 60.0 per cent of the series. Medical inductions were successful in 69 patients, and bag inductions succeeded in 21, two of which were therapeutic abortions. In combination with medical induction, the membranes were artificially ruptured in 44 successfully induced cases.

The Deliveries

Including abortions, delivery was spontaneous in 244 (81 per cent). Twenty-one had forceps deliveries, and 34 (11.3 per cent) were sectioned. Two patients died undelivered.

Fetal Outcome

In the 301 pregnancies analyzed, 186 babies, or 61.8 per cent, were discharged alive. There were eight early abortions (2.7 per cent), 38 late abortions

and previable prematures (12.6 per cent), 53 stillbirths (43 antepartum and 10 intrapartum; 17.6 per cent), and 16 neonatal deaths (5.3 per cent).

Since the hypertensive mother's chance for a living baby is a practical consideration, we have analyzed some of the factors associated with fetal loss.

Initial Blood Pressure.—The data in Table I, line 11, show that the higher the initial pressure, the greater is the fetal mortality. Browne and Dodds[1] had 25 patients in whom the initial blood pressure was 150/100, or more. Only eight (32 per cent), had living babies, and no patient with an initial systolic pressure greater than 180 bore a living child. In our series, 31 women were known to have prepregnancy pressures of more than 180; 16 of these had living babies. Of 75 women with prepregnancy systolic pressures of less than 200, four out of five had living babies. One patient, three years post partum and two years before conception of the pregnancy analyzed, consistently had a pressure of 210/120 to 220/130 over several months of observation. She was seen in the eighth week of gestation, with a pressure of 210/128, which she maintained. Pregnancy was allowed to continue until the twenty-eighth week, at which time it was interrupted because severe pre-eclampsia had supervened. A 790 Gm. child was born, and it lived.

The Midpregnancy Blood Pressure.—A rise in blood pressure during the second trimester is most ominous for the fetal prognosis. There were 106 patients whose second trimester blood pressures could be compared with earlier readings. In the 11 patients showing midpregnancy rises in pressure, only one (mentioned above) had a living baby; thus the fetal mortality was 91 per cent. In 53 patients whose blood pressure remained constant (within 20 mm. Hg), the fetal loss was 28.3 per cent. The mortality was 21.4 per cent in the 42 cases where the maternal blood pressure dropped in the second trimester.

Blood Pressure Near Time of Delivery.—The higher the blood pressure near delivery, the greater is the fetal loss. In analyzing the times of fetal death, we unexpectedly found that only neonatal deaths increase regularly with increments in the hypertension. Table V summarizes the relation of the blood pressure to the fetal outcome. Apparently our more severe hypertensives did not have a tendency to abort spontaneously.

TABLE V. THE BLOOD PRESSURE NEAR DELIVERY IN RELATION TO THE FETAL OUTCOME IN 301 HYPERTENSIVE PREGNANCIES

AVERAGE SYSTOLIC BLOOD PRESSURE, MM. HG	CASES	DISCHARGED LIVING (PER CENT)	EARLY ABORTION (PER CENT)	LATE ABORTION AND PREVIABLE (PER CENT)	STILLBIRTHS		NEONATAL DEATHS (PER CENT)
					ANTEPARTUM (PER CENT)	INTRAPARTUM (PER CENT)	
140 to 159	108	81.5	0.9	7.4	6.5	1.8	1.8
160 to 179	75	64.0	2.7	16.0	9.3	5.2	2.7
180 to 199	61	45.9	6.6	11.4	27.8	1.6	6.6
200 to 219	33	45.5	3.3	18.2	15.1	9.0	9.0
More than 220	24	29.2	0.0	20.8	29.2	0.0	20.8
Totals	301	61.8	2.7	12.6	14.3	3.3	5.3

Proteinuria.—The appearance of proteinuria is unfavorable for the fetus. In the patients showing only insignificant amounts, or no proteinuria, the fetal loss was 31 per cent. With pathologic degrees of proteinuria up to 4 Gm. per liter, the fetal mortality was 40 per cent. Greater degrees of proteinuria carried a fetal death rate of 56 per cent.

Renal Function.—In assessing the role of renal functional impairment in fetal loss, we have excluded cases with superimposed toxemia. We do this because: (a) superimposed toxemia increases the fetal mortality, and (b) such toxemia may depress the urea clearance somewhat. In the 126 nontoxic preg-

nancies where the patients concentrated their urines to 1.022 or higher, there were 30 fetal deaths, or 23.8 per cent. In the 82 pregnancies where the patients failed to concentrate as high as 1.022, there were 36 fetal deaths, or 43.9 per cent—nearly twice the rate in the former group.

Urea clearances were done in the patients who failed to concentrate to 1.022 or higher. There were 11 pregnancies in 11 patients, where the clearances were less than 70 per cent. Nine of the babies were lost, a mortality rate of 81.8 per cent—nearly three and one-half times the rate in pregnancies where the urinary specific gravities reached or exceeded 1.022.

Superimposed Toxemia.—In the nine eclamptic pregnancies, six babies were stillborn and two died in the neonatal period. The 81 pregnancies with superimposed pre-eclampsia gave rise to 44 babies that lived. There were 31 stillbirths and six neonatal deaths. Thus, the fetal loss in the 90 toxic pregnancies was 50 per cent. We may contrast the 173 pregnancies carrying past the twenty-fourth week and uncomplicated by superimposed toxemia; here the fetal mortality was 18.5 per cent—a little more than one-third the rate in the toxemic pregnancies.

Fetal Weights.—Once the fetus attains a weight of 2,500 Gm. its chances of survival do not seem to be improved materially by allowing the pregnancy to continue. The data in Table VI show no significant differences in the fetal mortality rates in the weight classes above 2,500 Gm. Apparently the hazards of neonatal death in the smaller babies are offset by the danger of stillbirth in continuing pregnancies. In all weight groups, the loss by stillbirth exceeds the neonatal mortality. There were 160 babies weighing more than 2,500 Gm. Of these, 12, or 7.5 per cent, were stillborn. Of the 148 live births three, or 2 per cent, succumbed.

TABLE VI. FETAL WEIGHTS AND MATERNAL BLOOD PRESSURE NEAR DELIVERY, IN RELATION TO FETAL MORTALITY*

BIRTH WEIGHT:	WEIGHT UNKNOWN			LESS THAN 1,000 GM.		1,001 TO 1,500 GM.		1,501 TO 2,000 GM.		2,001 TO 2,500 GM.		2,501 TO 3,000 GM.		3,001 TO 3,500 GM.		3,501 GM. OR MORE	
SYSTOLIC BLOOD PRESSURE, MM. HG		CASES	MORTALITY (PER CENT)	CASES	MORTALITY (PER CENT)	CASES	MORTALITY (PER CENT)	CASES	MORTALITY (PER CENT)	CASES	MORTALITY (PER CENT)	CASES	MORTALITY (PER CENT)	CASES	MORTALITY (PER CENT)	CASES	MORTALITY (PER CENT)
Less than 180	3	27	100.0	8	87.6	13	38.4	12	18.3	29	6.9	49	2.0	46	4.3		
180 to 219	10	18	100.0	14	57.2	9	55.6	11	27.3	10	20.0	10	20.0	8	25.0		
More than 220	3	6	83.3	1	100.0	5	100.0	0	–	4	0.0	5	40.0	0	–		
Totals	16	51	98.1	23	69.6	27	55.6	23	17.4	43	9.3	64	9.4	54	7.4		

*There were 16 cases, all deaths, with no recorded weights; nearly all less than 1,000 Gm.

Sterilization and Therapeutic Abortion

Twenty patients were sterilized, twelve at the time of section, and eight post partum. Three therapeutic abortions were done. One patient with malignant hypertension died six weeks after the abortion. Another patient, a rather mild hypertensive, succumbed to a cerebral hemorrhage six years and four months later. The third patient is still alive fourteeen years later, having borne a living child in the interim.

Immediate Maternal Mortality

There were six immediate maternal deaths, an incidence of 2.0 per cent, or almost ten times the rate for the whole hospital experience. Four of these deaths

occurred in the first pregnancy definitely established as hypertensive, while two died in later pregnancies. Briefly, the deaths may be summarized as follows:

1. N. W., History No. 1812. Negro, aged 41 years, gravida xi, para x, previous pregnancies toxic. Nonpregnant blood pressure in 1936, 162/92 to 170/100. Admitted Aug. 3, 1937, in thirty-fifth week of pregnancy, in labor and bleeding. Blood pressure 194/120, marked edema. Sectioned for severe abruptio placentae; baby stillborn. She was anuric for four days, but established a good diuresis. Died on the twelfth postoperative day, of peritonitis. No prenatal care.

2. B. H., History No. 34990. Negro, aged 21 years, gravida i, para 0. At four months gestation, blood pressure 240/150, no proteinuria, no edema, no eyeground changes. One month later she developed edema, blurring of vision, retinal hemorrhages and exudates, and proteinuria known to be of acute onset. Blood pressure had remained nearly constant. She aborted spontaneously at twenty-three weeks, and died on the fifth postpartum day of a pulmonary embolus. The patient's mother had died in childbirth, cause unknown.

3. E. M., History No. 36091. White, aged 41 years, gravida x, para ix. She was sent to the hospital on Oct. 11, 1938, after six convulsions, by a local physician who stated that her blood pressure had been 220 from early in pregnancy. She at once delivered a seven-month stillborn baby, and died the following day of circulatory failure incident to eclampsia.

4. M. B., History No. 21739. White, aged 36 years, gravida vi, para iii. Eclampsia in 1927; hysterotomy in sixth month, for severe toxemia in 1928, mild pre-eclampsia in 1935, nonpregnant hypertension (140/92) in 1936, severe toxemia in 1938 (another hospital), early abortion in February, 1939. Admitted in labor, in twenty-ninth week of gestation, Dec. 24, 1939. Blood pressure 170/138, 4 plus proteinuria, marked edema, and the whole train of severe toxemic symptoms. She had many petechial spots on her face and hands. There were old and new retinal hemorrhages. She delivered a stillbirth the same day, and died on the eighth postpartum day of bacterial endocarditis and anuria. No prenatal care. Her mother had died in childbirth, cause unknown.

5. E. P., History No. 32643. White, aged 23 years, gravida ii, para i (stillbirth with hypertensive toxemia included in this series). Nonpregnant hypertension, 185/120 to 220/130. A private patient, admitted Nov. 6, 1940, in seventh month of pregnancy. Blood pressure 250/150, proteinuria 3 Gm. per liter (of very recent onset), and no complaints. On the ninth day of bed rest, she had a fatal cerebral hemorrhage, and died undelivered.

6. M. R., History No. 25403. See Case Report. Died of hemorrhage incident to a rupture of the uterus while in early labor. Negro, aged 34 years.

Late Puerperal Deaths

There were seven late puerperal deaths, occurring from six weeks to four months post partum. Four of these were uremic deaths in malignant nephrosclerosis, at the ages of 28, 31, 32, and 42 years. They were post partum six weeks (following therapeutic abortion), three months, four months, and ten weeks respectively. Another patient, who had long-standing rheumatic heart disease, died of "acute endocarditis" three months post partum, aged 32 years. One died of acute ventricular failure six weeks post partum, aged 36 years. The last one died nine weeks after the delivery of her fourth hypertensive pregnancy, aged 28 years. She had laid down for a nap, and was found dead.

All late puerperal deaths are known to be included here, since we have traced *every* patient to 1946.

Discussion

Our analysis of the 301 hypertensive pregnancies certainly establishes the dangers of pregnancy itself—one woman in 23 died either immediately or within four months after delivery, and two in five lost their babies. The total maternal mortality was 20 times that for the whole hospital experience, the fetal loss was increased nearly tenfold, and the incidence of toxemia was multiplied by seven.

Of the 13 immediate and late puerperal deaths, four were uremic, and it is quite possible that pregnancy may have accelerated the renal decompensation. However, one of these deaths occurred six weeks after a therapeutic abortion done at sixteen weeks. In another case, there was some evidence of the onset of malignant hypertension before conception. The other two patients were not seen until late in pregnancy, at which time their urea clearances were less than 30 per cent. The times of onset of the malignant phase of hypertension are unknown in these two cases, although both had had severe hypertension two and three years, respectively, before conception.

Taking the 13 deaths together, eight were probably associated with the hypertensive disease, while five were attributable to intercurrent causes.

While pregnancy very definitely jeopardizes the hypertensive woman, the hazards are not great in two out of three cases. Two-thirds of our patients escaped superimposed toxemia. In this group, there were no immediate maternal deaths, and one of the two late puerperal deaths was of intercurrent causation. The fetal loss was 18.5 per cent. Among the one-third of patients who had pregnancies complicated by the superimposition of toxemia, there were six immediate maternal deaths (6.67 per cent), and five late puerperal deaths, giving a total maternal mortality of 12.2 per cent—ten times that in the uncomplicated hypertensive group. The fetal loss was exactly 50 per cent—almost three times that in the cases escaping superimposed toxemia.

If only we could determine which patients would escape pre-eclampsia or eclampsia, a good prognosis for pregnancy could be offered to two out of three hypertensive women. If the toxemia *causes* the damage done, then the prompt termination of a hypertensive pregnancy at the first sign of developing toxemia should protect the patient. If this were so, then perhaps any hypertensive woman could be given a chance at pregnancy, should she desire it. While her risks would be greater than those of a normal woman, there is a good chance that close supervision would give her a living baby.

The fetal loss of 38 per cent is greater than the mortality reported by Reid and Teel[7] (21.9 per cent), or by Browne and Dodds[1] (16.2 per cent). However, Browne and Dodds' standard for hypertension was 130/70. Wellen[8] recorded a stillbirth incidence of 36.2 per cent, and Mussey, Hunt, and Sluder[5] found a fetal loss of 30.6 per cent.

The midpregnancy drop in blood pressure has a very practical importance for diagnosis. An appreciable number of our hypertensives had perfectly normal blood pressures over several weeks of the second and third trimesters. Had their earlier hypertensive pressures been unknown, they would be classifiable

as pre-eclampsia, since they had acute rises in pressure after the twenty-fourth week of gestation, earlier known pressures having been normal. This factor confuses the interpretation of permanent hypertension apparently left as a sequel of "pre-eclampsia." Prepregnant blood pressure recordings in such cases are rarely obtainable, and the diagnosis of pre-eclampsia must depend upon readings taken during pregnancy—usually in the latter half.

Summary and Conclusions

From the opening of the hospital in October, 1931, through 1944, there were a total of 218 patients in whom recorded blood pressures establish the diagnosis of "hypertensive toxemia," as defined by the American Committee on Maternal Welfare.

A detailed analysis has been made of the 301 pregnancies in which these patients have been seen.

The gross fetal loss: In prior pregnancies, 35 per cent; in first hypertensive pregnancy, 38 per cent; in subsequent pregnancies, 40 per cent.

Of 47 sisters of these hypertensive patients, who delivered here, 45 per cent had at least one toxic pregnancy.

Nearly 40 per cent of the hypertensive patients showed drops in the blood pressure in midpregnancy.

Proteinuria of some degree occurred in half of the pregnancies.

Renal function was normal in 93 per cent of the pregnancies.

Premature separation of the placenta occurred in 5.6 per cent of the pregnancies.

Fetal loss increased with: higher initial blood pressure, second trimester rises in blood pressure, higher pressures near delivery, decreased renal function, proteinuria, and superimposed toxemia.

There were six immediate maternal mortalities (2.0 per cent), and seven late puerperal deaths. Thus the mortality was 20 times that of the whole hospital experience.

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MORBIDITY ASSOCIATED WITH INDUCTION OF LABOR*

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SINCE the causative factors of the onset of labor are still unknown, caution should be noted in evaluating any procedure which seems to have precipitated labor. For example, about 5 per cent of the patients hospitalized for inductions at St. Louis Maternity Hospital went into spontaneous labor before any procedures were carried out.

Hamblen[1] states that we do not know why labor begins. Reynolds[2] believes that the onset of labor is due to alterations in estrogen-pituitary-progestin balance influenced by uterine distention.

The most helpful work comes from Lyon[3] in his search to find changes concurrent with the initiation of labor. By using the new glucuronic acid method, the NaPG excretion in the urine decreases preceding the onset of labor similarly in those cases at term, postmature, and in premature groups. There is a positive correlation between an extensive fall of conjugated pregnandiol and the onset of labor. Also, there is strong evidence of a marked drop in available progesterone preceding the onset of normal labor.

With this new knowledge available, a different interpretation may be placed on studies of induced labor. Lyon[3] shows there is a 58 per cent decrease of sodium pregnandiol glucuronidate excretion in the urine during the four days before delivery takes place. The greatest changes take place within the 48 hours to 72 hours preceding termination of the third stage of labor.

Morton[4] of Lynch's Clinic reports induction of labor by means of artificial rupture of the membranes, castor oil and quinine, and nasal pituitrin. Guttmacher,[5] in 1931, and Slemons,[6] in 1932, report further on induction of labor by means of artificial rupture of the membranes, showing that the latent period and duration of labor are shorter whenever the cervix is dilated, and naturally effaced at the time the membranes are ruptured artificially for induction of labor. Stern,[7] Plass,[8] and Mathieu and Holman[9] all show the low morbidity and excellent results obtained by induction. It must be remembered, however, that their material was selected from abundance and that their skill and working conditions were of the best.

In 1925 a unit history system was started at Barnes Hospital. This enabled a review of obstetric cases with their subsequent admissions to Barnes Hospital to be made. For this reason, and because of intern experience with many of these cases, the author chose to review all inductions from June, 1925, to July, 1927, at Barnes Hospital. This series constituted 160 cases, and the material was limited to only viable babies at the onset of the induction. No cases were taken under thirty-six weeks' gestation, and for the most part the elective rupture of membranes was used but rarely. Incidence of induction

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was 8.3 per cent of parturient hospital admissions of at least thirty-six weeks gestation. The combined maternal and fetal morbidity was 20 per cent.

The St. Louis Maternity Hospital cases from the years 1928 to 1934, inclusive, were chosen for the second group of induction of labor. These 140 cases were not a series, but a selection, chosen to show the morbidity associated with combining the older technique of pituitary extract, castor oil, quinine, bags, and bougies, with the addition of artificially rupturing the membranes as an added procedure when failure to induce occurred. Incidence of induction was 13.5 per cent of parturient hospital term admissions. The combined maternal and fetal morbidity was 40 per cent.

The third group of cases comprised all the inductions for the year 1944 at the St. Louis Maternity Hospital. No cases were taken under 36 weeks gesta-

History number
Age
Gravida
Paragravida
Complications:
  1st Trimester
  2nd Trimester
  3rd Trimester
Estimated date of confinement
Date admitted for induction
Urine
Blood pressure
Weight gained
Weight on admission
Fetal position, size in cm.
Indications for induction
Induction of Labor
Started
  Date
  Hour
Castor oil
Castor oil, quinine
Ruptured membranes, spontaneous or artificial
Infundin
Estrogen
Ergot
Bag
Bougies
Manual dilatation of cervix
Labor
1st Stage
  Date
  Hour
  Duration
  Uterine contractions
  Sedation
  Infundin
  Presenting parts cervix
2nd Stage
  Date
  Hour
  Duration
  Uterine contractions
  Sedation
  Infundin
  Presenting parts cervix
  Date
  Hour of delivery
3rd Stage
  Date
  Hour
  Duration
  Bleeding
  Ergot-Infundin
  Placenta-Schulze-Duncan
  Total hours of labor
  Anesthetic
  Description of delivery
Condition of Baby at Birth
  Spontaneous cry
  Spontaneous respiration
  Tracheal catheter
  Medical respiratory and cardiac stimulants
  Hot and cold baths
  Cyanosis
  Pallor
  Twitching
  Birth weight
Maternal, First 14 Days of Puerperium
Temperature
  Average
  Minimum
  Maximum
Catheterization
Bleeding
  Average
  Moderate
  Excessive
Endometritis, acute
Date out of bed
Date discharge
Total hospital days
Total postpartum days
Postpartum and Latent Gynecological Complications
Condition of mother at time of discharge
Chronic subinvolution of uterus
Retrodisplacement of uterus
Cervical lacerations
Cervicitis with erosion
Condition of baby at time of discharge
Sequelae, comments

TABLE

	MORBIDITY GRAV. I 41 % INCIDENCE 33½%			MORBIDITY GRAV. II PARA. I 15%			MORBIDITY GRAV. II PARA. 0 35%		
	GREEN	YELLOW	RED	GREEN	YELLOW	RED	GREEN	YELLOW	RED
1925-26-27 (160 cases) Series	6	14	13	16	22	3	1	3	4
1928-34 (140 cases) Selected	8	10	34	16	7	6	4	3	2
1943 (50 cases) Selected	47	13	21	38	8	10	3	1	2
1944 (150 cases) Series									
Total (500 cases)	Green 61	Yellow 37	Red 68	Green 70	Yellow 37	Red 19	Green 8	Yellow 7	Red 8

226 Green—No Morbidity
146 Yellow—Morbidity not caused by induction of labor

372
128 Red—Morbidity, Maternal and Fetal, incurred by induction of labor
Combined Maternal and Fetal Morbidity 25%
10.6% of hospital admissions induced, parturients of more than 36 weeks' gestation

tion, as in the other two groups. Incidence of induction was 10.2 per cent of parturient hospital term admissions for the private service; 0.8 per cent for the ward service. This series comprised 150 cases. The combined maternal and fetal morbidity was 20 per cent. Fifty additional cases were selected from a 1943 group of patients, taken largely from a controlled private service, and induced by elective rupture of the membranes and pituitary extract, only if needed. The combined maternal and fetal morbidity was 8 per cent. This gave a total of 500 cases in all, which were subjected to critical analysis by obtaining the following information from each case.

Each case was then studied as to its morbidity. A green, a yellow, and a red marker were used to denote—no morbidity; morbidity, but not likely due to the induction of labor; and red indicating morbidity, thought to be caused by the induction of labor. This first general classification showed 226 green cases with no morbidity, 146 yellow cases with morbidity not caused by induction af labor, for example, acute upper respiratory infections, gastrointestinal disturbances, unexplained antepartum fever, etc. were listed. There were 128 red cases which made a maternal and fetal morbidity of 25 per cent for the 500 cases studied. Fetal morbidity, such as intracranial injury, stillborn, when a fetal heartbeat was noted at the beginning of labor, and prolapsed cord, were included in these 128 red cases. However, fetal death from erythroblastosis or icterus neonatorum was not counted as morbidity and was classed as either green or yellow. The standard of morbidity was 100.4° F. or 38° C. for any two consecutive days of postpartum hospital stay, and was a minimum basis for classification as a red case. Postpartum hemorrhage, 500 c.c. to 700 c.c. plus; ruptured uterus, deep cervical and parametrial laceration, separation of the symphysis, and damage to bladder or rectum also

TABLE I

MORBIDITY GRAV. III PARA. II 18%			MORBIDITY GRAV. III PARA. 0-I 19%			MORBIDITY GRAV. IV PARA. III 10%			MORBIDITY GRAV. IV PARA. I-II 25%			MORBIDITY GRAV. V+ PARA. III+ 19%		
GREEN	YELLOW	RED	GREEN	YELLOW	RED	GREEN	YELLOW	RED	GREEN	YELLOW	RED	GREEN	YELLOW	RED
13	16	5	5	3		5	5		2		2	4	10	4
6	2	9	3	1	3	1	7	2	2			8	5	5
18	1	1	5	4	2	2			2			11	1	
Green 37	Yellow 19	Red 15	Green 13	Yellow 8	Red 5	Green 8	Yellow 12	Red 2	Green 6	Yellow	Red 2	Green 23	Yellow 16	Red 9

constituted morbidity, however, practically all such cases had the minimum requirement of temperature elevation.

The first general grouping of cases were as to the gravida and gravida-para combinations. There were 166 primagravida women and 334 multipara. Approximately 33⅓ per cent of the 500 inductees were primagravida. There were 61 green cases, 37 yellow cases, and 68 red cases of this primagravida grouping. At a glance this shows the danger of inducing a woman with her first pregnancy, 41 per cent morbidity.

When the age incidence was brought into the picture there was a definite higher morbidity in the younger women, in the teen age to 20-year group, and in the 20 to 25 years of age group. Further observation divided the cases into six general groups of classification as follows:

1. Toxemias	47 cases	21 Red	44% Morbidity	9% Incidence
2. Disproportion	31 cases	19 Red	60% Morbidity	6% Incidence
3. Ruptured membranes (not followed by induction of labor within 12 hours)	14 cases	11 Red	80% Morbidity	3% Incidence
4. Post mature as to estimated date of confinement	109 cases	27 Red	25% Morbidity	20% Incidence
5. Ante estimated date of confinement	168 cases	31 Red	18% Morbidity	33% Incidence
6. Estimated date of confinement	131 cases	19 Red	14% Morbidity	26% Incidence
Total	500 cases	128 Red	25% Morbidity	99% Incidence

Taking the first group of toxemias, it was noted that in 1925 to 1927 there were 130 cases classified as toxemias which were not induced, and 20 cases which were induced, which means that only 13 per cent of the toxemias of thirty-six weeks' gestation or more required induction in their management. Practically all observers have noted the ease with which toxemias of pregnancy are usually induced by medical means. The other groups, 1928 to 1934, and 1943 to 1944, showed 14 per cent and 10 per cent, respectively, that required induction. It has been suggested that the toxemia produces infarction in the placenta which has the tendency to terminate pregnancy. However, all observers list toxemias as a cause for induction of labor, if and when management of the cases calls for termination of pregnancy. There is no uniform agreement in the literature on management of the other five general groupings.

TABLE II. GROUP 1; TOXEMIAS INDUCED
(Which were 9% of 500 cases studied)

1. Method of induction	Ruptured membranes and oxytocic		85%
	Mechanical induction	Bags	32%
		Bougies	15%
	Cesarean sections		0%
2. Average hours of labor and birth weights	Morbidity cases averaged	17 hours and 2,800 Gm.	
	Nonmorbidity cases averaged	8 hours and 3,100 Gm.	
3. Acquired injury to cervix (Lacerations)	Morbidity cases incidence		75%
	Nonmorbidity cases incidence		23%
4. Morbidity 44% combined maternal and fetal	29% Gravida—i 15% Multipara	Maternal morbidity	30%
		Maternal mortality	0%
		Fetal morbidity	14%
		Fetal mortality	14%
5. Latent sequelae	No lesions		14%
	Lesions		86%

Subsequent record on 53% of cases.
No subsequent record on 47% of cases.
Diagnosis and Procedures: Retrodisplacement of uteri; cervicitis with laceration; parametritis; complete hysterectomy; suspension of uterus; cauterization of cervix; conization.

TABLE III. GROUP 2; DISPROPORTION BETWEEN FETUS AND PELVIS, CONTRACTED PELVIS
(Which were 6% of 500 cases studied)

1. Method of induction	Ruptured membranes and oxytocic		71%
	Mechanical induction	Bags	16%
		Bougies	50%
	Cesarean sections		1%
2. Average hours of labor and birth weights	Morbidity cases averaged	32 hours and 3,200 Gm.	
	Nonmorbidity cases averaged	9 hours and 3,200 Gm.	
3. Acquired injury to cervix (Lacerations)	Morbidity cases incidence		80%
	Nonmorbidity cases incidence		40%
4. Morbidity 60% maternal and fetal combined	35% Gravida—i 25% Multipara	Maternal morbidity	31%
		Maternal mortality	3%
		Fetal morbidity	29%
		Fetal mortality	23%
5. Latent sequelae	No lesion		18%
	Lesion		82%

Subsesuent record on 48% of cases.
No subsequent record on 52% of cases.
Diagnosis and Procedures: Retrodisplacement of uteri; cervicitis with laceration; parametritis; phlebitis; complete hysterectomy; cauterization of cervix.

The morbid cases had an average labor of seventeen hours, over twice the hours of labor in the nonmorbid cases, which averaged eight hours. Birth weights of the babies averaged 300 Gm. less in the morbid cases. Cervical laceration was acquired in 75 per cent of the morbid cases and in 23 per cent of the nonmorbid cases. Fetal morbidity and fetal mortality were the same, 14 per cent. Nonmorbid cases had more matured babies and were induced closer to the time of spontaneous initiation of labor.

The second grouping is that of "disproportion between fetus and pelvis; contracted pelvis." In 1925 to 1927 at Barnes Hospital, the series of 16 cases induced for disproportion between the fetus and pelvis is in contrast to an incidence of three cases induced in the larger series of 1943 to 1944 at the St. Louis Maternity Hospital. The use of Caldwell-Malloy x-ray pelvimetry, at or near the expected date of confinement, has furnished a more accurate means of classifying the pelvic disproportion to the particular fetal head under consideration. The use of the low cervical cesarean section with transverse incision (advocated by Phaneuf[10]) after a "trial of labor" rather than a "test of labor" has given such satisfactory results that this is now a method

of choice. Fetal mortality and morbidity and the high incidence of puerperal infection have been shown by Douglas and Stander[11] to occur with prolonged labors. The difficulty of inducing labor in this group is in contrast to the toxemia group. Stander[11] has also pointed out that the morbidity and mortality have been decreased when long labors have been allowed to terminate spontaneously without operative interference. When disproportion is the problem, such a happy termination cannot be counted upon. Connen and Jones[12] showed that 20 per cent of interference had been unnecessary as the size of the children had been overestimated, or that subsequent labor resulted in spontaneous delivery of babies definitely larger than those born following induction. This was true in five cases of this series. It seems therefore that induction of premature labor, in the management of a contracted pelvis, should not be considered a justifiable procedure. However, termination of pregnancy after the child has attained full maturity, with an attempt at medical induction and if failure occurs, a repetition within a few days might be justified, but cannot be recommended as a procedure of choice. If the membranes are ruptured, one must be prepared to do a low cervical cesarean operation within twenty-four to thirty-six hours after rupture of the membranes if labor is not successful.

Birth weights of babies here were the same average for morbid and nonmorbid cases. The hours of labor were almost four times as long in the morbid cases as in the nonmorbid group, with an average of nine hours. Eighty per cent of the morbid and 40 per cent of the nonmorbid cases acquired cervical laceration. A high maternal and fetal morbidity and mortality condemn induction of labor unless it is instituted very near to the onset of spontaneous labor, which was not the picture in this grouping of disproportion between fetus and pelvis.

The third general grouping "spontaneous rupture of the membranes not followed by active induced labor within 12 hours," fortunately consisted of only 14 cases out of the 500 studied, but the high morbidity of 80 per cent stresses the danger in such a situation. There were two patients with placenta previa and one marginal placenta in this group. This of course increased the morbidity, however, a prolapsed cord, Bandl contraction ring of the uterus, intracranial injury, a case of Dührssen's incision of the cervix, and two cesarean sections

TABLE IV. GROUP 3; SPONTANEOUS RUPTURE OF THE MEMBRANES NOT PRODUCTIVE OF LABOR WITHIN 12 HOURS

(Which were 3% of the 500 cases studied)

1. Method of induction	Oxytocic		85%
	Mechanical induction	Bags	43%
		Bougies	0%
	Cesarean sections		15%
2. Average hours of labor and birth weights	Morbidity cases averaged	25 hours and 3,000 Gm.	
	Nonmorbidity cases averaged	20 hours and 3,800 Gm.	
3. Acquired injury to cervix (Lacerations)	Morbidity cases incidence		90%
	Nonmorbidity cases incidence		50%
4. Morbidity 80% maternal and fetal combined	50% Gravida—i 30% Multipara	Maternal morbidity	58%
		Maternal mortality	21%
		Fetal morbidity	22%
		Fetal mortality	20%
5. Latent sequelae	No lesion		14%
	Lesion		86%

Subsequent record on 64% of cases.

No subsequent record on 36% of cases.

Diagnosis and Procedures: Placenta previa; postpartum hemorrhage; terminal ruptured uteri; separation of symphysis; retrodisplacement of uteri; cervicitis with laceration; parametritis; ligation of uterine arteries; cervical branches; cauterization of cervix, uteri, for laceration; pessary for retrodisplacement.

with one maternal death occurred in addition. Fortunately, spontaneous rupture of the membrane is usually followed by labor or it is possible to induce labor without too much difficulty.

DePuy,[13] from a study of failure in induction of labor, concluded that in elective induction, when labor fails to follow rupture of the membranes and attempts to stimulate pains with oxytocics fail, the patient should be put to bed and let alone since there may be an interval of from two to four days before labor starts. It is pointed out that the complications listed by DePuy[13] which follow rupture of the membranes for the induction of labor are in cases where the cervix is not prepared for the advent of labor. This should serve as a warning that if the membranes are ruptured electively for the induction of labor the patient must be at the threshold of labor, or a high morbidity incidence will occur. Plass[8] showed, in comparing spontaneous rupture of the membranes with elective rupture of the membranes, that labors of more than thirty hours duration were two and one-half times as common in the elective rupture figures than in the spontaneous rupture of the membranes. However, the great majority of his spontaneous ruptures were in cases that were in active labor. Morton and Adair[14] concluded from a clinical study of premature rupture of the membranes in which there were 536 primiparas and 464 multiparas, that infant mortality is higher if delivery occurs after a latent period of fifty-five hours or more. Seventy-one cases had artificial rupture of the membranes. One hundred eighty-two cases required castor oil, quinine, pituitrin, or the use of a bag in combination. Of 63 patients who were febrile, 41 had some type of operative procedure. Eighty patients with membranes ruptured over 24 hours, not operated upon, gave 6.4 per cent morbidity. The total morbidity for the 1,000 cases was 6.3 per cent. The general hospital morbidity rate was 7.7 per cent. These findings might tend to obscure the real danger found in the rarer conditions of failure to induce labor as recorded in the 14 cases in this series of 500 cases studied. It will be noted that in the 1943 to 1944 series, there were no cases of spontaneous rupture of the membranes not followed by active induced labor within a 12-hour period. This shows a better selection of cases of those nearer the time labor would have started spontaneously.

In addition to the morbidity of 80 per cent as shown in Table IV, there was a maternal mortality of 21 per cent and a fetal mortality of 20 per cent. Ninety per cent of the cases acquired cervical laceration in the morbid group, and 50 per cent in the nonmorbid group. The hours of labor averaged twenty-five hours for the morbid and twenty hours for the nonmorbid group. Birth weights of the babies in the nonmorbid group were 800 Gm. higher than of those in the morbid group.

Caution should be exercised in selecting cases for induction by using this method of rupturing the membranes, since failure of labor to start leads to a prohibitive morbidity. However, when a mistake is made, the use of sulfonamides and penicillin prophylactically instead of forcing labor by oxytocics and mechanical means might give a lower morbidity rate. Intrauterine fetal infection, especially lung infection of colon bacilli etiology, was noted in this group.

The fourth general grouping "postmature as to estimated date of confinement, three days to twenty-one days plus," showed that 109 cases out of the 500 studied gave a 25 per cent morbidity, this figure was rather surprising, as one could logically reason that such patients should be prepared for labor and that induction should produce less unfavorable results. However, uterine dystocia was present in about 10 per cent of the cases. On the whole, the birth weights were above the average. Rathbun[15] showed that from a study of 250 cases of postmaturity, the period of postmaturity was longer on the average for stillborn infants 24.4 days beyond term, as against 19.6 days for

TABLE V. GROUP 4, POSTMATURITY AS TO ESTIMATED DATE OF CONFINEMENT
(3 days to 21 days plus)
(Which were 22% of 500 cases studied)

1. Method of induction	Ruptured membranes and oxytocic		97%
	Mechanical induction	Bags	14%
		Bougies	2%
	Cesarean sections		3%
2. Average hours of labor and birth weights	Morbidity cases averaged	26 hours and 3,600 Gm.	
	Nonmorbidity cases averaged	13 hours and 3,600 Gm.	
3. Acquired injury to cervix (Lacerations)	Morbidity cases incidence		55%
	Nonmorbidity cases incidence		20%
4. Morbidity 25% maternal and fetal combined		Maternal morbidity	16%
	11% Gravida—i	Maternal mortality	0%
	14% Multipara	Fetal morbidity	9%
		Fetal mortality	4%
5. Latent sequelae	No lesions		40%
	Lesions		60%

Subsequent record on 44% of cases.

No subsequent record on 56% of cases.

Diagnosis and Procedures: Separation of symphysis; parametritis; cervical laceration; retrodisplacement of uterus; hysterectomy complete; abdominal for retrodisplacement of uterus; suspension; cauterization and conization of cervix; pessary.

live babies. He concludes there is no more need for fear that the fetus will be lost in utero without cause than exists at term. Postmaturity occurred 1 in 13.2 deliveries in his series. It would be an assumption that, because labor does not start within two or more weeks after the estimated date of confinement, that the baby is postmature. Cornell[16] states that patients thirty-five days over the estimated date of confinement have been known to give birth to babies weighing 3,300 Gm. to 4,200 Gm. showing a wide variation in fetal size. There is an equally wide variation in the series of cases here presented, as to fetal weights. One case of a 4,600 Gm. child was induced by means of ruptured membranes, resulting in a ten-hour labor, without birth injury or injury to the cervix, as compared with another case of a 3,100 Gm. child induced by means of ruptured membranes and infundin, producing a ten-hour labor, resulting in intracranial birth injury and a lacerated cervix. Postmaturity as to estimated date of confinement is not a reliable diagnosis. It is extremely difficult to correlate the fetal size with the calculated date of confinement.

The fifth general classification "induced more than two days before the estimated date of confinement," thirty-six to thirty-nine weeks inclusive, was tabulated as follows: thirty-six weeks, 2 per cent incidence; thirty-seven weeks, 25 per cent incidence; thirty-eight weeks, 65 per cent incidence; thirty-nine weeks, 8 per cent incidence. There were 168 such cases out of the 500 cases studied and there was a morbidity of 18 per cent. It was noted that morbid cases had average lower birth weights than the nonmorbid cases studied in this grouping. This was taken to mean, together with the slightly longer hours of labor, that these patients were not at the threshold of labor. Please bear in mind that these cases were electively induced without indications of toxemia, or disproportion, or spontaneous rupture of the membranes. Ninety per cent were between thirty-seven and thirty-nine weeks of gestation and were for the most part convenient inductions. Most of the morbidity was due to intracranial injury and prolapsed cord. Cases that were not pushed, but were allowed to be failures of induction in which spontaneous labor later occurred in the second or third attempt at induction some four to five or ten days to two weeks later, usually resulted in no morbidity unless the membranes had been ruptured. It is thought that the lower morbidity rate in this series, as compared with the morbidity rate of the preceding group, namely, postmature as to date of confinement, could be explained as follows: in the

TABLE VI. GROUP 5; INDUCED MORE THAN TWO DAYS BEFORE THE ESTIMATED DATE OF CONFINEMENT

(36 weeks 2%) (37 weeks 25%) (38 weeks 65%) (39 weeks 8%)
(Which were 33% of 500 cases studied)

1. Method of induction	Ruptured membranes and oxytocic		95%
	Mechanical induction	Bags	14%
		Bougies	2%
	Cesarean sections		0%
2. Average hours of labor and birth weights	Morbidity cases averaged	14 hours and 3,200 Gm.	
	Nonmorbidity cases averaged	10 hours and 3,500 Gm.	
3. Acquired injury to cervix (Lacerations)	Morbidity cases incidence		70%
	Nonmorbidity cases incidence		25%
4. Morbidity 18% maternal and fetal combined	10% Gravida—i 8% Multipara	Maternal morbidity	11%
		Maternal mortality	0%
		Fetal morbidity	7%
		Fetal mortality	4%
5. Latent sequelae	No lesion		40%
	Lesion		60%

Subsequent record on 43% of cases.

No subsequent record on 57% of cases.

Diagnosis and Procedures: Phlebitis; parametritis; cervical laceration; prolapse of uterus; retrodisplacement of uterus; hysterectomy complete; abdominal for uterine suspension; operation for cystocele and rectocele; Manchester operation; perineorrhaphy; cauterization of cervix; conization of cervix.

TABLE VII. GROUP 6; ELECTIVE INDUCTION AT ESTIMATED DATE OF CONFINEMENT—PLUS OR MINUS TWO DAYS

(Which were 26% of the 500 cases studied)

1. Method of induction	Ruptured membranes and oxytocic		98%
	Mechanical induction	Bags	4%
		Bougies	0%
	Cesarean sections		2%
2. Average hours of labor and birth weights	Morbidity cases averaged	20 hours and 3,300 Gm.	
	Nonmorbidity cases averaged	8 hours and 3,400 Gm.	
3. Acquired injury to cervix (Lacerations)	Morbidity cases incidence		70%
	Nonmorbidity cases incidence		20%
4. Morbidity 14% maternal and fetal combined	8% Gravida—i 6% Multipara	Maternal morbidity	10%
		Maternal mortality	2%
		Fetal morbidity	4%
		Fetal mortality	2%
5. Latent sequelae	No lesion		40%
	Lesion		60%

Subsequent record on 35% of cases.

No subsequent record on 65% of cases.

Diagnosis and procedures: Phlebitis; parametritis; retrodisplacement; myoma of uterus; cervicitis with laceration; prolapse of uterus; vaginal plastic operation for cystocele and rectocele; cystitis; hysterectomy complete; abdominal for suspension of uterus; cauterization and conization of cervix.

former group, failure to induce was taken more seriously and mechanical means were resorted to, giving a higher incidence of cervical laceration and much longer labors, whereas with this group, failure to induce was not taken seriously and another attempt was made nearer to the threshold of spontaneous labor.

The last general classification was "elective induction at estimated date of confinement, plus or minus two days." There were 131 such cases, an incidence of 26 per cent, giving a morbidity rate of 14 per cent. This is the lowest morbidity rate of the six general classified groups, and it is quite logical that elective induction at the estimated date of confinement, excluding toxemias, disproportion, and spontaneous rupture of membranes which failed to induce within a twelve-hour period, would yield the lowest morbidity.

It is to be expected, as pointed out in 1944 by Gillett[17] reporting 1,000 cases of elective induction by rupture of the membranes, that the optimum time for elective induction was as close to term as possible. He used the following points in determining the time for elective induction: first, calculated date of confinement; second, fundal measurements; third, the ripeness of the cervix; the latter being the most important. Nonengagement of the fetal head was considered an absolute contraindication to artificial rupture of the membranes, because of the increased risk of the cord prolapsing. He claims that a well-effaced cervix which was thin and soft was a reliable indication of impending labor in both primiparas and multiparas. In the multiparas these cervical changes were not always present before the onset of labor. One hundred per cent induction occurred within a twelve-hour period. He states that the average latent period, from the time of rupturing the membranes to the onset of labor, was approximately one hour for all cases. The average duration of labor in the primiparas was six hours, and three hours for the multiparas. An oxytocic agent (pitocin) was used in his series in order that the procedure of induction occur in all cases.

The maternal mortality in his series was zero, the puerperal morbidity was 5.1 per cent, no stillbirth occurred, and he explains this fact by limiting induction to normal patients only. Fetal distress, prior to induction, was another contraindication to inductions. Neonatal mortality was 0.8 per cent. Four cases had pneumonia, congenital anomalies occurred in two cases, hemorrhagic disease in the newborn in one case, and an undetermined cause of death in another. He concludes that the best technique for inducing labor is a hot soapsuds enema, hypodermic pitocin, and low rupture of the membranes. There were 642 multiparas and 358 primiparas, totaling 1,000 patients reported in Gillett's series.

Holman[18] states in a personal communication, that he has had a combined experience of over 2,000 cases of induction of labor with statistics on morbidity and infantile mortality practically identical with those published in 1937. There were no maternal deaths, and a maternal morbidity of 5.3 per cent. Fetal mortality, uncorrected, was 3.5 per cent. He used pituitary extract and after one or two doses, routinely ruptured the membranes. Pentobarbital is used to keep the patient tranquil and free from pain.

Plass[8] reports 1,000 consecutive normal parturient women with cephalic presentations, in which spontaneous rupture of the membranes occurred, called Group 1, and compared them with 1,000 normal women in whom labor was induced by elective rupture of the membranes, called Group 2. Twenty-five per cent of the patients in each group had postpartum temperature elevation of 100.4° F. or above. The incidence of true puerperal morbidity, as indicated by the presence of fever for more than one day, was slightly higher in Group 2, the induced series, and may be explained by the inevitable vaginal manipulation.

There were, however, no serious infections, and persistent fevers were recorded in each group to about the same extent. He states that labors induced by artificial rupture of the membrane do not differ materially from those which start spontaneously. Intrapartum infections were twice as frequent in the induced series, and this increase may be attributed to the procedure. The duration of the labor showed that there was a definite increase in the number of "thirty hour or more labors" among the women in the Group 2 induced series. In each division of the multigravidas, the percentages of longer labors were higher in the induced group than in Group 1. He states that the birth process tends to be either slightly shortened or somewhat prolonged when labor is induced electively by premature rupture of the membranes, but gives no clue as to the factors producing either tendency. Plass[8] states that it was

difficult to evaluate the condition of the cervices after spontaneous and elective rupture, because of "out-of-city" patients; however, the experience gained from routine speculum examinations when patients were discharged from the hospital eight to ten days after delivery confirmed the observations of Schumann[19] that dry labor does not increase the incident or degree of cervical injury.

The question of cervical laceration and injury to the cervix has been of particular interest and study for the past sixteen years and was one of the factors in arousing interest in this study of morbidity associated with the induction of labor. It seems that the only reliable clinical means available at the present time as to whether a patient is crossing the threshold of labor is the condition of her cervix. One year ago a patient entered the St. Louis Maternity Hospital with a full-term abdominal pregnancy. Those in charge of the case reported the patient to be in labor, the cervix to be soft, effaced, and dilated, although there was no presenting part within the uterus and there was no uterine bleeding. This condition of the cervix has been noted and was referred to by Cornell and Lash.[20] The theory of the onset of labor as having a hormonal etiology which causes softening, thinning, and dilatation is borne out by clinical observations. It would therefore be expected that, if labor were induced when such changes were present, labor would proceed normally without laceration or injury to the cervix, not because of the method of inductions used, but because of the prepared condition of the lower uterine segment and cervix.

Hamilton,[21] in his article on "Preliminary Stage of Labor," points out that when labor seems to be in process without the above noted changes in the cervix and when intervention occurs during this period, morbidity results. Unnecessary cesarean sections for cervical dystocia are done during this period, whereas if the patient were given sedation, normal labor would occur at a later date.

Calkins,[22] in his article, "Predicting Length of Labor; First Stage," states that it is interesting to consider the etiology in variation in the cervix and in uterine contractions. The cause is not anatomic. It is almost certainly physiologic. The etiology of the onset of labor is inextricably involved in both cervical consistency and effacement, and uterine contractions. Only when this physiologic factor has been found can the least favorable patients be prepared to enter labor with unresisting cervix and good uterine contractions.

With these points in mind, it is readily seen that patients induced by Holman,[9] Plass,[8] Gillett,[17] and others[4] referred to are a literally hand-picked selected group and that no increase in morbidity should be expected unless there is an error in judgment as to the case selected for induction not being ready for impending labor.

During the past three years no ward patients at the St. Louis Maternity Hospital have been induced except for toxemia. All ward patients are followed in the Clinic and referred to the Cervicitis Clinic if cervical laceration or lesions are found. With the elimination of pituitary injections, the incidence of cervical lacerations has been reduced an estimated 75 per cent.

Severe cervical lacerations occurring with an induced labor constituted a morbidity factor in these 500 cases of induced labor reported. In multiparas with cervical laceration and no history of previous induction of labor, laceration was not recorded as morbidity unless definite evidence of new deep laceration was reported with the induced labor.

The subgrouping of only morbid cases into acute endometritis, hemorrhage, and transfusion incidence gives the picture shown in Table VIII.

The incidence of acute endometritis and hemorrhage is almost the same except in the contracted pelvis, pelvic disproportion (B) Group. Here the

greatest concerted effort was made to force labor and delivery, and most of these cases were before the common practice of blood transfusions. Manipulation which introduces infection, and blood loss which lowers the resistance to infection brings about morbidity. Failure to keep the uterus well contracted contributes to both infection and blood loss. In no group did the incidence of hemorrhage exceed the incidence of acute endometritis by more than 1 per cent.

TABLE VIII. MATERNAL MORBIDITY; MORBIDITY CASES ONLY

CLASSIFICATION GROUPS	ACUTE ENDOMETRITIS 15% INCIDENCE	HEMORRHAGE 12% INCIDENCE	TRANSFUSION 33% INCIDENCE*
A Toxemia	21% of all A cases	17% of all A cases	37%* of all A cases
B Contracted pelvis, pelvic disproportion	26% of all B cases	10% of all B cases	0%* of all B cases
C Ruptured membranes, not productive of labor within 12 hours	30% of all C cases	30% of all C cases	75%* of all C cases
D Postmature as of the estimated date of confinement	4% of all D cases	5% of all D cases	16%* of all D cases
E Antemature—more than 2 days before estimated date of confinement	5% of all E cases	5% of all E cases	50%* of all E cases
F ± 2 days of the estimated date of confinement	5% of all F cases	5% of all F cases	14%* of all F cases

*Percentage of hemorrhage cases requiring transfusion.

In the toxemia and contracted pelvis groups the incidence of infection was greater than the hemorrhage incidence. In ruptured membranes not followed by induced labor within twelve hours, the highest incidence of acute endometritis and hemorrhage was found and the percentage was identical. Douglas and Davis[23] state that: "If labor continues sufficiently long with ruptured membranes, clinical signs of infection will always occur, even in the absence of pelvic examinations or other possible outside sources of infection. The development of intrapartum infections does not imply that the postpartum course will be febrile, or the patient classified as having morbidity by any of the standards commonly employed. If following premature rupture of the membranes no labor whatever develops, and the patient is kept at rest in bed, then infection is unlikely to occur." They also point out that infections may be decreased by control and restoration of blood loss. Sulfadiazine and/or penicillin given early may be efficacious, while late in the course of the disease they are less effective.

Royston[24] states, "The widespread, injudicious use of pituitary injections during labor has undoubtedly increased maternal morbidity (from tears), and fetal morbidity (from intracranial injuries)."

Thompson[25] states, "There are and can be no indications for elective induction of labor. The method proposed by Slemons[6] has many meritorious features. The requirements are logical; the technique is simple; the results are usually most gratifying. However, contraindications exist unless (1) term has been reached, (2) the head is engaged, (3) the cervix is effaced, and (4) dilatation has begun. When one has questioned himself closely and has satisfied himself that these requirements have been met, then, and only then, may

elective induction be considered without undue assumption of risk. Evasion of these requirements has given rise to hazards ranging from prolongation of the 'latent period,' difficulties with resistant cervices, emergency cesareans, and intrapartum infections to stillbirths and maternal death."

It has been established that there is morbidity associated with the induction of labor under certain conditions. The results of a study of those cases which failed to induce, 13 per cent of the 500 cases presented, are shown in Table IX.

TABLE IX. FAILURE TO INDUCE (2 TO 14 DAYS PLUS) OF ALL INDUCED—13% OF 500 CASES

Of all attempts to induce contracted pelvis (pelvic disproportion)	35% failed
Of all attempts to induce toxemia patients	25% failed
Of all attempts to induce ruptured membranes not productive of labor within 12 hours	21% failed
Of all attempts to induce the antemature more than two days before the estimated date of confinement	11% failed
Of all attempts to induce the postmature as of the estimated date of confinement	9% failed
Of all attempts to induce ± two days of the estimated date of confinement	9% failed

The groups contracted pelvis-pelvic disproportion; toxemia; ruptured membranes not productive of induced labor within 12 hours; and antemature, more than two days before the estimated date of confinement, show from 35 per cent to 11 per cent of all such cases failed to induce, while 9 per cent of the postmature and 9 per cent of the plus or minus two days of the estimated date of confinement failed to induce. The greatest failure to induce occurred in cases which were the furthest removed from the natural onset of spontaneous labor.

Now, if the 67 cases out of the 500 cases which failed to induce are totaled as to incidence, the antemature more than two days before the estimated date of confinement show that 28 per cent failed to induce. Next were the toxemia cases and those of two days plus or minus of the estimated date of confinement. Then the contracted pelvis-pelvic disproportion with 16 per cent incidence of failure to induce. Next came the postmature as of the estimated date of confinement, with 15 per cent incidence; and last, 4 per cent incidence of failure for the ruptured membrane group. With the exception of ruptured membranes, the lowest, and antematurity the highest of failure to induce, the other groups varied by 3 per cent, two of the groups were the same per cent, and the other two groups varied by 1 per cent. Again there is strong evidence of some basic factor underlying the cause for the onset of labor in each case.

Now if the incidence of failure to induce is broken up into two days. four days, seven days, and fourteen days of failure, the percentages are 34, 27, 20, and 18. Only the ruptured membranes not followed by induced labor within twelve hours showed no failure to induce past a two-day period. However, the morbidity of this group was 80 per cent. The highest percentage of failure occurred within the two-day and four-day groups, but the incidence of seven-day and fourteen-day failure varies only from 1 to 2 per cent. All this would indicate some basic factor in failure to induce any given case.

For comparison 500 cases of natural spontaneous labor were studied as to the time labor started in reference to the estimated date of confinement. These were 250 ward cases at the St. Louis Maternity Hospital and 250 private patients at the same hospital.

As to the onset of spontaneous labor, 27.7 per cent were from minus one to minus ten days before the estimated date of confinement; 6.9 per cent were

TABLE X. THOSE 67 CASES WHO FAILED TO INDUCE

28%	Incidence were—antemature—more than 2 days before estimated date of confinement (the least concerted efforts were made here)
18%	Incidence were—toxemia
18%	Incidence were—± 2 days of the estimated date of confinement
16%	Incidence were—contracted pelvis, pelvic disproportion (the greatest concerted efforts were made here)
15%	Incidence were—postmature as of the estimated date of confinement
4%	Incidence were—ruptured membranes not productive of labor within 12 hours
99%	Total

TABLE XI. INCIDENCE OF FAILURE TO INDUCE

	2 DAYS FAILURE	4 DAYS FAILURE	7 DAYS FAILURE	14 DAYS FAILURE
Toxemia	5%	5%	4%	4%
Contracted pelvis, pelvic disproportion	3%	6%	3%	4%
Ruptured membranes not productive of labor within 12 hours	4%	0%	0%	0%
Postmature as of the estimated date of confinement	6%	3%	4%	2%
Antemature—more than 2 days before estimated date of confinement	13%	4%	6%	4%
± 2 days of the estimated date of confinement	3%	9%	3%	4%
Total 99%	34%	27%	20%	18%

on the estimated date of confinement; 37 per cent were from plus one to plus ten days after the estimated date of confinement. Therefore, from ten days before to ten days after the estimated date of confinement, a total of 71.6 per cent of labor occurred.

At the estimated date of confinement the average birth weight was 3,580 grams. This birth weight was not surpassed until the average of 3,680 Gm. (only 100 grams more) was attained by the plus sixteen to plus twenty days after the estimated date of confinement group. The average of the plus one day to the plus fifteen days after the estimated date of confinement was less than the average weight of those babies born on the estimated date of confinement. Now the weights of the plus twenty-one days to plus twenty-five days were less than the birth weights of the estimated date of confinement group. This would probably indicate a mistake in calculation of the expected onset of labor.

All of those born before the estimated date of confinement averaged less than the estimated date of confinement group or plus days group following the calculated date, but many individual birth weights were 3,910 to 4,300 Gm. It is clearly shown that the calculated date of confinement proposed by Naegele is of little value in fixing the date for the onset of labor or determining the size of the newborn.

Now when the hours of labor are tabulated it is interesting to note that the averages vary from fourteen hours for the most immature to eight hours for the most postmature. Nine hours was the average for those labors which occurred at the estimated date of confinement and those which were plus one to plus five days after the calculated date. However, the group which had the highest birth weights, plus sixteen days to plus twenty days past the estimated date of confinement, did have an average of twelve hours for the labors. The longest labor in this group was twenty-two hours as against sixty hours for the two most immature groups. These shorter hours of labor with the

TABLE XII. AN ANALYSIS OF 500 CASES: 250 WARD, 250 PRIVATE, WHOSE LABORS WERE SPONTANEOUS, NOT INDUCED

ESTIMATED DATE OF CONFINEMENT		BIRTH WEIGHTS	HOURS OF LABOR
−25 Days to −21 Days	4.6%	(2,350-3,880 Grams) Average 3,090	(3-60 Hours) Average 14
−20 Days to −16 Days	5.0%	(2,790-4,350 Grams) Average 3,260	(3-60 Hours) Average 14
−15 Days to −11 Days	7.0%	(2,700-3,950 Grams) Average 3,110	(2-25 Hours) Average 10
−10 Days to − 6 Days	13.4%	(1,700-3,900 Grams) Average 3,260	(2-32 Hours) Average 11
− 5 Days to − 1 Day	14.3%	(2,940-4,110 Grams) Average 3,400	(3-26 Hours) Average 10
E.D.C.	6.9%	(2,950-4,330 Grams) Average 3,580	(2-21 Hours) Average 9
+ 1 Day to + 5 Days	19.4%	(2,750-4,410 Grams) Average 3,480	(2-24 Hours) Average 9
+ 6 Days to +10 Days	17.6%	(3,031-4,100 Grams) Average 3,470	(2-31 Hours) Average 10
+11 Days to +15 Days	3.7%	(3,170-3,690 Grams) Average 3,430	(4-19 Hours) Average 11
+16 Days to +20 Days	3.7%	(3,425-4,290 Grams) Average 3,680	(5-22 Hours) Average 12
+21 Days to +25 Days	4.6%	(3,010-3,800 Grams) Average 3,460	(3-20 Hours) Average 8

27.7% minus 1 to minus 10 days before estimated date of confinement.
37.0% plus 1 to plus 10 days after estimated date of confinement.
6.9% on the estimated date of confinement.
Total of 71.6% within a plus or minus 10 days of the estimated date of confinement.

greater birth weights were seen in all cases which did not have morbidity associated with the induction of labor. This was taken to mean that those cases which showed no morbidity were at the threshold of spontaneous labor when labor was induced.

There has been no attempt to compare the induced 500 cases with the above 500 control cases except as to birth weights and hours of labor. The calculated morbidity of the spontaneous labor group was about 10.5 per cent combined maternal and fetal, as against 25 per cent combined maternal and fetal for the induced labor group. It is felt that more information is obtained as to causative factor in morbidity if different groups of induced labors are studied. For example, the highest morbidity of any group of the induced cases was 80 per cent for the ruptured membranes not followed by induced labor within twelve hours; and the lowest morbidity of 14 per cent occurred in cases induced at estimated date of confinement. When membranes were ruptured in this group the cervix was effaced and dilatation had begun; the head was well fixed or engaged within the pelvis and induced labors proceeded as normal spontaneous labor because these patients were already in early labor when inductions were begun.

Discussion

The contention seems trite that only such patients that are entering the threshold of labor can be induced without morbidity caused by the induction, yet this is the plain conclusion from this study. The work of Lyon[3] referred to in the introduction would bear out this conclusion.

By courtesy of Dr. Willard Allen, a patient in his department whose pregnandiol excretion in the urine was being studied failed to induce with infundine injections until repeated attempts to induce with pituitary extract some forty-eight to seventy-two hours later were shown to have coincided with the fall in pregnandiol, at which time labor started and concluded successfully.

Unfortunately, the time consumed and expense involved make it for the present, at least, impossible to use pregnandiol excretion as a means of determining when labor will start. It may be asked if other oxytocics such as quinine, ergonovine, and methergen have any unique ability to induce labor.

Murphy[26] has shown with his study of uterine contractions with the Lorand tocograph the pattern of false labor and its relation to premature labor, that false labor may be followed by premature labor.

Lyon[3] shows a case of irritable uterus and placenta bleeding with a drop from NaPG of 70 mg. to 30 mg., from April 27 to April 30. A rise to 70 mg. again on May 3, and premature delivery May 14, after a fall to 10 mg. on May 12. It will be recalled that charts designed to show reason for failure to induce would indicate the frequency of forty-eight-hour intervals from the first attempt to a successful attempt at induction.

Marchetti, Kuder, and Fitch[27] selected 500 cases for study of the effect of antepartum administration of small doses of quinine. Labor was not shortened, and with primiparas it was lengthened. The percentage of patients who delivered before the expected day of delivery was slightly higher than in a control series. Adair and Davis[28] report that ergotocin gave inconclusive results for the induction of labor. Farber[29] reports 43 consecutive cases of induced labor with five failures when the new drug methergen is used. This preparation, he states, is similar to ergonovine but contains an additional CH_2 group. Here again the same principles would seem to apply as to the ability to induce.

Eastman[30] outlines the requirements to be met for induction in the diabetic patient as follows: A sterile vaginal examination is made to determine, (1) if the head is at or below the spines; (2) if the cervix admits easily one or two fingers, and (3) if the cervical canal is less than 1 cm. long. The infant must be between 3,000 and 3,500 Gm. in weight. Then the membranes are stripped back and ruptured. If the cervix is not favorable for induction and there is no urgency, the patient is allowed to go to term or to such a time as the cervix is favorable. If urgent, a cesarean section is done. This would seem to be the procedure of choice for all toxemias and diabetics.

Bouton[31] does not favor prematurely induced labor for the erythroblastic fetus, as attention is called to the possibility of increasing damage by labor. Whether this represents an actual hazard in practice remains to be seen, but it must be considered in weighing the relative merits of labor induction versus cesarean section.

Conclusions

1. It has been shown that there can be severe morbidity incurred with the induction of labor.

2. The increase in morbidity is caused by forcing labor before the cervix, lower uterine segment, and uterus have been prepared for labor.

3. The character and results of induced labor approach that of natural spontaneous labor only when the induced labor precedes by forty-eight hours or less the time when spontaneous labor would have occurred anyway.

4. This means that induction of labor has obstetric usage mainly in the management of the toxemia patient, including the diabetic.

5. For the management of contracted pelvis, pelvic disproportion, induction has little or no usage.

6. For the management of postmaturity, induction has little or no usage.

7. Induction of labor after spontaneous rupture of the membranes may be a dangerous procedure.

8. The morbidity incurred by induction of labor must be evaluated against any questionable advantages in such management.

9. Elective induction of labor, which would have occurred in twenty-four hours to forty-eight hours later, gives little or no morbidity.

10. Such elective induction is of little or no obstetrical advantage, but rather has convenience and order as its justification.

I desire to express my appreciation to Miss Bessie E. Taylor, Chief Historian in charge of record room at Barnes and St. Louis Maternity Hospitals, who made available the histories and data for statistical study, and to Dr. Seymour Monat, Resident at St. Louis Maternity Hospital, who tabulated the data on 150 cases of the 1944 series.

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Discussion

DR. EMMETT D. COLVIN, Atlanta, Ga.—It is interesting to note that 48 per cent of the inductions were for the termination of pregnancy, either "electively," in 26 per cent, or, because of postmaturity, in 22 per cent.

While this and other investigations indicate fairly satisfactory results following the elective induction of labor presumably at or near term, the procedure is sufficiently radical to warrant a thorough discussion of the subject.

The results of my experience with induction of labor are similar to the conclusions drawn by Dr. Roblee.

In recent years, there has been a strong tendency to broaden the indications for termination of pregnancy at or near term by elective induction of labor, usually by artificial rupture of the membranes alone or in combination with oxytocics. For example, in our University Hospital, the incidence of induction increased from 1 in 23 to 1 in 6 labors during the past four years. Among the attendants it was found that the incidence of induction for diplomates and nondiplomate specialists in obstetrics had not increased, but the per cent of inductions had precipitously increased among general practitioners who became specialists during the war years as a result of suddenly inheriting a large volume of obstetric cases. The characteristic haste of such attendants to induce simultaneously a group of cases at or near term in order to save time and secure rest is shown by their frequent resort to cesarean section, and also by the readiness with which they perform difficult operative deliveries or injudiciously rely upon oxytocic drugs to terminate labor rapidly. The inevitable result of such a meddlesome policy is trauma. It is my belief that all cases admitted into hospitals for induction of labor should be studied by a governing board prior to induction.

I am not an advocate of elective induction of groups of women for convenience. We have met the problem of added volume and consequent loss of rest by the formation of an obstetric group in which the members rotate in shifts through the hospital and office hours. Under this plan outlined by Bartholomew in "Utopian Obstetrics" the members of the group secure ample rest and sleep. Thus, in our practice elective induction is limited, with exceptional cases, to multiparous women whose previous labors were rapid and those whose residence is a considerable distance from the hospital. To me, the latter type of patient is always a problem.

If pregnancy and labor are still to be regarded as a physiologic process, the burden of proof for a successful outcome following elective induction of labor becomes a moral and legal responsibility of those who so boldly interfere and accept responsibility for the management of unexpected complications after labor has been initiated in a normal process.

No one will argue against the wisdom of inducing labor in complicated cases of pregnancy where experience has taught that pelvic delivery offers the greatest degree of safety for the mother and fetus.

Dr. Roblee's figures reveal a high incidence of cervical damage among the induced cases. When labor is induced, the possibility of cervical trauma must always be kept in mind, not alone from a standpoint of danger at the time sustained, but also from that of its behavior during subsequent deliveries.

I have always doubted the wisdom of induction of premature labor in the management of a case of contracted pelvis. The potential dangers of a prolonged latent period, the unpredictable behavior of the uterine muscle, the unprepared cervix, and the immature fetus, in addition to the limitation of pelvic space, all combine to predict trouble from the start. Dr. Roblee's figures of a combined maternal and fetal morbidity of 60 per cent, along with a 3 per cent maternal and 23 per cent fetal mortality, offers proof that it is far

from the ideal method in managing such cases. I believe that a policy of noninterference with pregnancy, a test of labor at term, and cesarean section at the properly selected time is much the better plan of management.

His statistics, revealing the high incidence of morbidity and mortality associated with induction of labor among cases in which the membranes had been ruptured twelve or more hours, are worthy of careful study. A combined maternal and fetal morbidity of 80 per cent along with a maternal and fetal mortality of 21 and 20 per cent, respectively, is indicative of the seriousness of the problem this type of case presents. Note that 15 per cent of these cases were delivered by cesarean section. I feel that cases presenting definite evidence of rupture of the membranes should not be left awaiting spontaneous onset of labor for an indefinite period of time. It is our policy to attempt to initiate labor in such cases within six to twelve hours following spontaneous rupture by medical induction. The administration of castor oil followed, if necessary, by pituitary extract intranasally or, if not effective, by minute doses hypodermically has given good results. It is important that such cases be spared surgical induction and that operative interference be reduced to a minimum in their management.

DR. ALBERT W. HOLMAN, Portland, Ore.—In 1935, my associate, Dr. Mathieu, and I reviewed our statistics on 750 cases of induction of labor with a control series of 750 cases of noninduced labor. I feel that one must differentiate between the medicinal and the mechanical types of induction. The results are just as different as in automobile accidents and typhoid fever. This is the third paper I have heard presented before this Association where bags, bougies, and oxytocics are lumped together in discussions of inductions of labor. You cannot figure them that way. Those done medically are very different from those done mechanically.

In our 750 cases of induced labor we had a fetal mortality of 0.9 per cent. We had no cases that did not go into labor. It makes a lot of difference whether the induction of labor is done by one trained person or whether left to the nurses in the delivery room, where perhaps one nurse will start an oxytocic, and after several injections another nurse will take over. I am making a plea for subsequent studies of induction of labor to differentiate between the medical induction and the mechanical induction of labor.

DR. M. PIERCE RUCKER, Richmond, Va.—I have induced labor by rupture of the membranes over 4,000 times. The record is shown in the table.

Unfortunately, there are included consultation cases. If I had not included those the two groups would have been more comparable. For instance, four of the six maternal deaths were in consultation cases, but more particularly there would have been a better distribution of the severe complications of pregnancy. I was surprised, for instance, to find that in placenta previa there were more cases in the uninduced group than in the amniotomy group. The cases for amniotomy were not selected unless there were complications present. In a normal case the patient herself elected whether she wanted the day set at or near term. In the complicated cases, however, I tried to do what I thought best. Had the consultation cases been eliminated, I feel that there would have been a higher percentage of placenta previas in the amniotomy group.

There were 4,045 amniotomy cases and 2,138 others. The neonatal deaths were 1.1 per cent in the amniotomy cases and 4.2 per cent in all others. Stillbirths were 1.1 per cent in amniotomy cases and 5 per cent in all others. There have been some unfavorable selection in the "all others" cases. There were more eclampsias and ablatio placentae, etc. in the "all others." There were four detached retinas, three in the amniotomy cases and only one in all others. What I wanted to point out was that the morbidity was not increased by amniotomy. There were only 160 cases with afebrile puerperium, or 3.9 per cent, in the amniotomy cases and 155, or 7.2 per cent, in the others.

The surprising thing was the prolapsed cord cases. There were only eight in the 4,045 amniotomy cases in comparison with 21 in the other cases.

PRIVATE CASES (INCLUDING CONSULTATIONS) FROM NOVEMBER, 1932, TO AUGUST, 1946

	NO. OF CASES	NEONATAL DEATHS	STILLBIRTHS	FEBRILE PUERPERUM	ECLAMPSIA	TOXEMIA	ABLATIO PLACENTAE	DETACHED RETINA	INVERSION OF UTERUS	SHOCK	PROLAPSED CORD	POSTPARTUM HEMORRHAGE	PHLEBITIS	CONSTRICTION RING	PLACENTA PREVIA	TWINS	MATERNAL DEATHS
Total	6,183	146 (2.2%)	154 (2.4%)	315 (5.0%)	24	106	61	4	3	12	29	58	19	125	93	37	6
Amniotomy	4,045	56 (1.1%)	47 (1.1%)	160 (3.9%)	11	75	23	3	2	6	8	35	7	75	35	15	4 Heart disease, congestive heart failure; Pre-eclampsia; Steiner's disease; Placenta previa
All others	2,138	90 (4.2%)	107 (5.0%)	155 (7.2%)	13	31	38	1	1	6	21	23	12	50	58	22	2 Sepsis, pneumonia; Ruptured uterus, hysterectomy, pneumonia

So I think these figures show that in carefully selected cases where you know the history and you have the measurements of the baby and the feel of the cervix to guide you, induced labor can be safely done. I agree with the essayist's conclusions about long labors. The figures, however, show that amniotomy at or near term can be done comparatively safely.

DR. J. BAY JACOBS, Washington, D. C.—I am probably in the same predicament as Dr. Rucker. I have not induced labor in as many women, but have done so over a long period of time. Dr. Roblee's presentation is timely and represents a good deal of work. I do not feel that the induction of labor in properly selected cases is too unwise, nor do I look for the death of the mother or fetus as a result of it. Ordinarily, I am no more concerned than if the patient had started in labor of her own accord.

Dr. Colvin's discussion was very practical. I believe we are all of the same opinion except that the incidence of morbidity, in his experience, seems rather similar to that of the essayist. I am sure that the frequency of morbidity, either maternal or fetal, in my experience is no greater than that of any comparable number of cases permitted to start in labor spontaneously and managed by the average man. I have noted no difference in morbidity between cases that I induce and those that go into labor spontaneously.

If cases were not carefully selected for induction, one would expect the general trend of results to be similar to those reported by the essayist, especially if they were induced by a large group of men, many of them not trained obstetricians. From that point of view, Dr. Roblee's results are not unexpected and not surprising.

A word might be said about the means of inducing labor. Of course, the bag and bougie are out of date, in my opinion. I see no indication for using them. Before the war, when quinine was available, I used to resort to a dose of castor oil, later followed by an enema and then small doses of quinine. Several hours later, I would rupture the membranes. There appeared to be no ill effects, although the use of an excessive amount of quinine is not justifiable. During the war, when quinine was not available, we soon found that merely a dose of castor oil, an enema, and rupture of the membranes at the proper time, and in properly selected cases, were satisfactory.

As to the duration of labor, it seems to be shorter than when labor starts spontaneously. Occasionally, one might encounter a protracted labor, but if the cases were selected with due caution, the incidence would probably be no greater than would ordinarily occur in any series of cases that were not induced.

In regard to the use of pituitrin for induction of labor, I have definite fear. I seldom use it, and when I do it is only over a short period of time and in small doses. The principal objection is that pituitrin frequently initiates rhythmic contractions which may persist indefinitely, causing more than average discomfort for the patient, and resulting in no change in the condition of the cervix, as determined by vaginal examination. For some reason, contractions caused by pituitrin do not seem to have the effect of ordinary uterine contractions. I feel that pituitrin frequently complicates matters.

Something might be said about the selection of cases for induction. These days we do not hesitate quite as much to induce labor as we formerly did. We are almost inclined to feel as we do in regard to the use of outlet forceps, except that one must proceed with greater caution. In my opinion, an important factor in selection of cases is the estimated date of confinement. If, upon abdominal examination, pregnancy appears to be at term and the estimated date indicates that the patient is not due for three or four weeks, I would certainly not induce labor, for in such a case, if induced before term, one might be surprised to find that the fetus is below average weight and may not appear mature. For that reason, I have a high regard for the estimated date of confinement. Induction should always be around this date. Another factor of importance is the position and degree of engagement of the head. It is rather essential that the head be engaged even though the danger of prolapsed cord might be slight and that there be no malposition which may complicate the mechanism of labor. It is necessary, also, for the patient to be cooperative and willing. For reasons that are evident, one should not try to convince a patient, in any manner, that labor should be induced, nor is it wise to institute any unnecessary procedure in a patient who displays fear. When there is any doubt as to the maturity of the fetus or the position of the head, I resort to the use of the lateral roentgenogram. I have frequently stated that in most cases the head has a tendency to engage with the biparietal diameter in the true conjugate. In my opinion, the size of the biparietal diameter is the most reliable indicator of fetal maturity. If this measurement is 9.25 cm., I feel that the fetus is mature. The babies I have delivered through induction of labor are all mature. I would say that they might average a trifle smaller than the average of those in my noninduced series at term, but it is not my purpose to deliver as big a baby as possible. For the benefit of the mother, I think an average size baby is sufficient. Finally, I wish to state that the most important factor relative to rupture of membranes for the induction of labor is the condition of the cervix. If the cervix is elongated or rigid the membranes should not be ruptured, and if the patient had been admitted to the hospital for that purpose, she should be sent home to await the onset of labor. Such a patient will usually return to the hospital in labor about two weeks later. Caution exercised in this manner will help to avoid protracted labor and all the concern that goes with it.

DR. A. N. CREADICK, New Haven, Conn.—A discussion of this subject has an infinite number of ramifications, one of which I have not heard emphasized by the discussants and which I would like to call attention.

It is obvious that a multipara with a partially dilated cervix, at term and with the head engaged, had better be brought into the hospital. The anesthetist had better be available because when you rupture the membranes delivery will be immediate. On the other hand, when you get a stout patient with a thick neck, swayback, midpelvic contraction, with a long, hard cervix, and you begin to pick and pick and pick, you get into trouble. I have seen my juniors make trouble for themselves and raise fetal mortality and maternal morbidity. It is those women who have indolent uteri, whose expulsive forces are inadequate, whose uteri are not readily irritated, who will have prolonged labors which are dangerous to the fetus. In 1915, Dr. Slemmons showed how the organisms penetrated the amniotic cavity. In 1922, I showed how the same organisms traversed the cord and gave the fetus a septicemia, and I recovered the organisms from the cord and from the empyema in the baby. That was accompanied by intrapartum fever.

DR. MILTON SMITH LEWIS, Nashville, Tenn.—I have had the opportunity to observe 500 private patients in whom labor was induced by the artificial rupture of the membranes: 461 cases were induced for the reason that they were at term and the "cervix was ripe" with two or more fingers' dilatation. The remaining 39 cases were induced in a similar manner for definite medical indications.

I am in complete accord with Dr. Jacobs that in properly selected cases artificial rupture of the membranes entails no serious increased risk to the mother or infant other than to be expected in a comparable group of natural labors. However, we do not believe that the routine rupture of the membranes should ever be employed just for the convenience of the patient or physician. But if the above criterion is strictly adhered to we are of the opinion that it is a simple, effective method of inducing labor.

It was interesting to observe that the latent period, from the time of rupture of the membranes to the appearance of definite uterine contractions, was less than one hour in 35 per cent; less than two hours in 30 per cent; less than four hours in 24 per cent. Or, in other words, 85 per cent, both primiparas and multiparas, had a latent period of less than four hours. Fifteen per cent had a latent period from six to twelve hours. Only one patient in the entire series had a latent period of more than twenty-four hours. We do not advocate the use of pituitrin after the rupture of membranes, however, we did use it in 11 instances where the pains were not as effective as we thought they should be.

Labor was definitely shortened; 36 per cent delivered in less than three hours; 39 per cent from three to six hours; 20 per cent from six to twelve hours, and 3 per cent from twelve to twenty-four hours. Only one patient had a labor of more than twenty-four hours. This was a case of uterine inertia in an occipitoposterior position, although she had a latent period of three hours.

Delivery was spontaneous in 45 per cent. Low forceps were used in 51 per cent; eleven required midforceps, and twelve labors were terminated by breech extraction.

There were no stillbirths. However, there were three neonatal deaths that occurred from twenty-four to forty-eight hours following delivery that were due to congenital atelectasis or, if you wish, pneumonia of the newborn, found at autopsy. All three were delivered spontaneously.

The total morbidity rate based on a reading of 100.4° F. at any time excluding the first twenty-four hours was three, or 0.6 per cent.

The incidence of laceration of the cervix observed at the six weeks' postpartum examination was 61, or 12.2 per cent. Twenty-one of these were repaired following a subsequent delivery.

The artificial rupture of the membranes in selected cases is a very useful method for the induction of labor, and the mortality and morbidity for the mother and infant can be kept exceedingly low.

DR. BUFORD C. HAMILTON, Kansas City, Mo.—Suppose a moratorium was declared on all unnecessary obstetric interference at this time. I think we will agree that for some time we have had a national obstetric interference inflation. Dr. Roblee has attempted to show us the dangers of induction of labor, and I know this is not his work or a reflection of his work. I am familiar with my own pathologic results in the induction of labor. I am also certain that others have had the same results.

DR. ROBLEE (Closing).—Dr. Holman will find the answer to his question in regard to relative morbidity of medical and surgical induction of labor as pointed out in these charts. Unlike Dr. Holman's series, these cases were not one doctor's, but were both ward and private patients of at least ten different men.

Dr. Rucker has shown low morbidity with induction of labor, but case selection is the answer. Dr. Jacobs induces only such cases in which there are no contraindications and in which there is cervical dilatation with head engagement. In my opinion these patients would have gone into labor within the next forty-eight hours without induction.

I wish to thank Dr. Creadick and Dr. Hamilton for their remarks and discussion. One criticism which could have been made was that in some of the charts insufficient numbers were recorded to permit of dogmatic conclusions. However, regardless of the groupings in all cases, the averages showed that nonmorbid patients had shorter hours of labor with above average or average birth weights for the babies; whereas the morbid patients showed longer hours of labor with lower than average birth weights for the babies. This means that the nonmorbid patients were at the threshold of labor when induction was instituted.

One last point. It so happens that three patients at the St. Louis Maternity Hospital were being studied as to their sodium pregnandiol glucuronidate excreted in the urine. Induction of labor in these cases was a failure until repeated efforts coincided with a fall of NaPG of 70 mg. to a 10 mg. excretion; confirming the work of Lyons, and also substantiating the forty-eight hour interval of incidence of failure to induce as shown in these charts.

THE TREATMENT OF PELVIC TUBERCULOSIS IN THE FEMALE BY RADIATION THERAPY BASED UPON EXPERIMENTAL EVIDENCE IN THE ANIMAL AND CLINICAL RESULTS IN THE HUMAN*

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THE treatment of pelvic tuberculosis in women, which lends itself to medical, surgical, or radiologic considerations, has been subjected to considerable controversy.

It is the purpose of this paper to consider the radiologic aspects of therapy in this disease relative to experimental studies in the animal and clinical investigations in the human.

Roentgen-ray therapy for genital tuberculosis was introduced by Bircher in 1908. According to the original report of Bircher, roentgen-ray therapy is indicated primarily (a) in those cases with adhesive or plastic peritoneal tuberculosis in which operation offers but little help, (b) in cases with cachexia in which operation is contraindicated, (c) in cases which refuse operation, and (d) in slight and benign cases. Cases in which roentgen-rays are to be used secondarily include (a) those in which the exudate reappears soon after operation, and does not disappear within fourteen days, and (b) all cases in which the symptoms return after operation.

Among the many reports favoring this type of therapy—alone or combined with surgery—may be mentioned Bumm, Krönig, and Zweifel in Germany; Schauta in Vienna; Solomons in Ireland; and Ford, Polak, and Jameson in the United States.

Since Bircher's original paper, Martius, Kolischer, and Gibert feel that roentgen-ray therapy should be extended to include all types of pelvic tuberculosis. While others, such as Edling, Weibel, and Pestalozza believe roentgen-ray therapy has its greatest indication as a postoperative measure following conservative or radical surgery. This group does not feel that it is a question of the roentgen-rays versus surgery, but a combination of the two methods.

The antagonist contends that radiation therapy of pelvic tuberculosis in the human is of no great therapeutic value and leads to (1) dissemination of the tuberculous process, (2) fistulous tract formation, (3) intestinal obstruction, and (4) that lymphocytic destruction by the roentgen rays leads to a breakdown in the healing process. It occurred to me that some of these criticisms might be answered by our findings at the University of Wisconsin General Hospital; not only by clinical observations of patients with this disease treated by roentgen-ray exposure in our clinic, but also by producing the pelvic disease in the laboratory animal and subjecting it to roentgen rays.

It was decided to produce pelvic tuberculosis experimentally in the female dog and subject these animals to roentgen-ray therapy in order to observe

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its effect. Such a procedure entailed a good many technical difficulties both from the standpoint of bacteriology and roentgen-ray administration. These problems were overcome through the advice and invaluable assistance of Paul F. Clark, Professor of Bacteriology, and Ernst A. Pohle, Professor of Radiology.

Dogs of comparable physical make-up were selected, and each weighed about 12 kilograms. The selection of these dogs was particularly important from the standpoint of roentgen-ray administration.

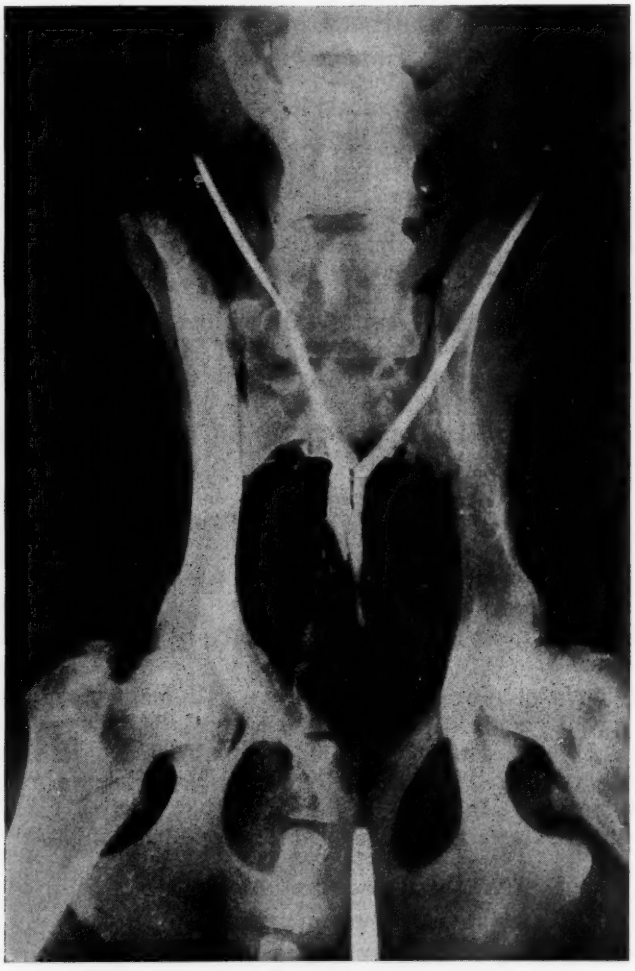

Fig. 1.

A strain of attenuated bovine tubercle bacilli was selected, which tended to produce localized nonprogressive lesions which appeared suitable for this research.

As to the choice of tubercle bacilli (human or bovine), the difference in reaction would be purely relative which should not materially alter any experimental conclusions.

Fig. 1 shows a normal uterus of a dog which has been injected with lipiodal and x-rayed.

In the technique of injecting the dog's uterus with tubercle bacilli, the abdominal cavity was opened and both horns of the uterus were tied off at their distal ends by black silk, and a third strand of silk tied off the uterus from the vagina. The uterus was injected with a tuberculin syringe, and between ½ to 1 c.c. of the bacterial suspension was usually injected. The number of tubercle bacilli per field was found to be between 25 and 100. The opening at the site of the needle withdrawal was treated with phenol.

Fig. 2 shows a uterus of a dog which has been injected with tubercle bacilli, and demonstrates the marked enlargement of both horns and vaginal portion. There was also present a moderate amount of adhesive and exudative reaction. This specimen compared with Fig. 1 shows the marked pathologic changes macroscopically. A biopsy was positive for tuberculosis.

Fig. 2.

A second laparotomy was usually performed about two months after the initial injection, and the genital organs were inspected for gross signs of tuberculosis and confirmed by biopsy. Laparotomies were performed about every two months thereafter.

Interestingly enough in some instances, the pelvic pathology, following the infection, appeared to be the adhesive and exudative types, while in others the genital organs were perfectly free with little exudative reaction. In some cases there was undoubtedly a secondary inflammation. Only cases in which the disease was confined to the pelvis were used in this series.

Roentgen-ray therapy was instigated at different time intervals relative to the diagnosis and extent of the disease in order to make the investigation more complete.

It was necessary to determine accurately the x-ray distance for roentgen therapy in an average size dog. This was done by killing a dog, injecting

the uterine horns with methylene blue, and then completely freezing the dog. Following this procedure a pelvic section was made.

Twenty dogs were used in this investigation in which the tuberculous process was limited to the pelvis.

Table I shows the number of series administered to the dogs as compiled by the Department of Radiology. A series consisted of one treatment each week for six weeks. The interval between series was approximately one month.

Tables II and III show in detail the roentgen-ray therapy given to several of these dogs.

TABLE I

DOG NUMBER	NUMBER OF SERIES OF TREATMENT	
2	1	
4	1	
6	4	
14	3	
27	2	
28	2	
31	1	had only 5 treatments of first series. Too sick to finish. Died with sponge in abdomen.
33	1	
34	5	
36	4	
37	4	
39	1	
41	4	
42	1	
43	3	
44	1	
45	3	
46	2	
47	2	
48	2	

TABLE II

X-ray over pelvis; 50 r posterior—100 r anterior. Field approximately 8 by 5½ to 6 cm. varying with size of dog; 0.5 copper + 1 aluminum filter; 6 milliamp; 180 kilovolt; 50 cm. distance.

	43, 45	45, 43
SERIES I	II	III
1st treatment—5.21.34	7.23.34	10. 1.34
2nd treatment—5.28.34	7.30.34	10. 8.34
3rd treatment—6. 4.34	8. 6.34	10.15.34
4th treatment—6.11.34	8.13.34	10.22.34
5th treatment—6.18.34	8.20.34	10.29.34
6th treatment—6.25.34	8.27.34	11. 5.34

TABLE III

X-ray: 75 r on two anterior areas (pelvis and abdomen—150 r). Field: abdomen, approximately 17 × 7 cm., pelvis as in Chart II; 0.5 copper—1 aluminum filter; 6 milliamp; 180 kilovolt; 50 cm. distance.

SERIES I (33, 34, 36)	II (34, 36)	III (34, 36)	IV (34, 36)
1st treatment—3.12.34	5.21.34	7.23.34	10. 1.34
2nd treatment—3.19.34	5.28.34	7.30.34	10. 8.34
3rd treatment—3.26.34	6. 4.34	8. 6.34	10.15.34
4th treatment—4. 2.34	6.11.34	8.13.34	10.22.34
5th treatment—4. 9.34	6.18.34	8.20.34	10.29.34
6th treatment—4.16.34	6.25.34	8.27.34	11. 5.34

Fig. 3*A* shows a considerable enlargement of both horns and vaginal portion of the uterus after injection. There was a slight amount of exudative and adhesive reaction present. Roentgen-ray therapy was started at two months. Twenty-four exposures were given with monthly intervals between series. At the end of a year a most remarkable result can be observed when Figs. 3*A* and 3*B* of dog 34 are compared. Microscopic sections from 3*B* showed no tuberculosis. The results shown in this dog, both before and after x-ray treatment, were representative of the series.

Eight control dogs were inoculated with bovine tubercle bacilli and given no roentgen-ray therapy. Four of the dogs succumbed rapidly to the disease within a period of seven months after inoculation. These rapid deaths were due not only to the disease itself but were hastened by starvation. The dogs that were given deep x-ray therapy appeared to take their food much better and their weight was maintained at a higher level. Two dogs died at nine

A. *B.*

Fig. 3.

and ten months, respectively, after their injections. One dog, apparently doing well at the end of thirteen months after the initial inoculation, had microscopic evidence of tuberculosis, even though the pelvis looked clear and the weight had been maintained. This dog was anesthetized at sixteen months, and sections of the pelvic organs showed an arrested tuberculosis. The eighth dog, sixteen months after the initial inoculation, had a pelvis which showed no miscroscopic evidence of tuberculosis. Four of these dogs in this series at autopsy showed a generalized miliary tuberculosis.

Of the twenty dogs that were inoculated, only nine could be carried over a two-year period because of the lack of space in the kennel and the demand for some of these dogs for use in the medical school for instructive purposes. Seven of the nine dogs showed an arrested tuberculosis, both by macroscopic and microscopic examination. The remaining two dogs still showed evidence of the disease.

In analyzing the results of these dog experiments it is undoubtedly clear that roentgen ray was beneficial in the therapy of pelvic tuberculosis. It is interesting to note that only one dog died while under therapy. In the whole series of twenty dogs inoculated and treated by x-ray, there was no doubt that radiation therapy tended to limit the disease to the pelvis, had a direct effect upon the absorption of the exudate, and reduction of the secondary inflammation. There is every reason to believe that many of these dogs might have developed intestinal obstruction if x-ray had not been given to the pelvis and obviated the factors which produce intestinal obstruction. Some of these animals had as many as eight laparotomies, and only in one instance was a fistula formed. The abdominal wounds healed rapidly with only an occasional superficial infection.

In comparing the control series with those treated by roentgen-ray therapy and the beneficial results obtained in the latter, the results are conclusive.

The favorable results obtained in the foregoing experimental data which were carefully scrutinized, not only by myself, but by Dr. John W. Harris, led us to believe that, contrary to the previous condemnation of the use of x-ray in the treatment of pelvic tuberculosis in the female, we should reconsider its use. We have therefore, been using roentgen-ray therapy in the treatment of pelvic tuberculosis in the female.

Out of the cases treated by roentgen-rays, I have selected those which I felt were most representative. In reviewing the case histories, I shall confine my reports to those facts which are considered pertinent and exclude irrelevant data, tending to maintain clarity with brevity.

Case Reports

CASE 1.—A. P., aged 19 years, Indian, was admitted to the hospital on Dec. 30, 1942. This patient had been hospitalized at the Hayward Indian Hospital on March 23, 1942, and the accompanying history from this institution showed that, dating from the birth of a child eighteen months previous to the time of her admission, the patient had been troubled with a vaginal discharge. On admission she complained of pain in the lower abdomen. She also had a small draining sinus lateral to the anal opening on the left buttock. Her physical examination at this time was essentially negative, except for lower abdominal tenderness on both sides. All laboratory tests were reported negative for the gonococcus and acid-fast organisms. The x-ray of her chest was negative, as were the agglutination tests. Her Wassermann was negative. Her temperature range was from 99.2° to 101.2° F. It was suggested by this institution that this patient have a complete gynecologic work-up. She was, therefore admitted to our service in the University Hospital and finally transferred to the tuberculosis service.

The following data were obtained while on our service: It was found on pelvic examination that the patient had a large right-sided pelvic mass which extended two fingerbreadths above the symphysis pubis with a mass of like size to the left. The uterus could not be separated from these masses. The vaginal secretions were cultured and found to be positive for tuberculosis. The tuberculin test was also positive. A piece of tissue taken from the anal fistula was also positive for tuberculosis. Repeated cervical, urethral, and vaginal smears were all negative. The Frei test was negative. Sedimentation test showed a graph

of an acute inflammatory process. A stereo of the chest on Jan. 1, 1943, showed small bilateral pleural effusions with some pleural thickening and nothing in these studies to indicate the etiology by changes in the lung field. During her stay in the hospital, the patient's temperature fluctuated between 101° and 102° F. with pulse rate between 100 and 120. Following these examinations the patient was transferred on Jan. 18, 1943, to the sanatorium because of her acute toxic condition.

The patient was readmitted to the hospital on April 7, 1944, after a year of sanatorium care. At this time the patient was less toxic, with a temperature running between 99° and 100° F. and a weight gain of twenty-eight pounds. An x-ray of the chest on April 11, 1944, showed no pleural effusion. Some pleural thickening obliterating the sulci on both sides and some thickening of the secondary interlobar fissure on the right, no positive parenchymal infiltration. The masses previously described in the pelvis were still present and were somewhat larger. On April 21, 1944, the patient had a colostomy because of obstructive bowel symptoms. Beginning May 15, and for four consecutive days, the patient was given 200 roentgens, with the H.V.L. in copper equaling 1.05 mm. to the anterior and posterior pelvis.

On July 18, 1944, the patient showed a marked regression of pelvic masses, and the uterus was well outlined for the first time, being about twice the normal size.

On Sept. 15, 1944, and for four consecutive days, the patient was given another series of deep x-ray consisting of four doses of 200 roentgens each, with H.V.L. in copper equaling 1.05 mm. to the anterior and posterior pelvis. She was discharged from the hospital following this series.

She was readmitted on Nov. 10, 1944, at which time she was examined by the gynecologic clinic and found to have a uterus of normal size with no palpable masses. She was discharged on Nov. 18, 1944.

The patient was readmitted on Feb. 6, 1945, at which time she was reexamined with the findings as follows: The large masses originally described had melted away and the fornices were clear. The uterus was normal, lying in the horizontal position, and the lesion about the rectum appeared to be healing. The results following deep x-ray to the masses were reported as remarkable.

CASE 2.—J. L., a 22-year-old, nulliparous patient developed pain in both lower quadrants. Temperature prior to operation was 99° to 100° F. by mouth. Weight was 100 pounds, a weight loss of ten pounds. The x-ray of the lungs was negative. The Wassermann was negative. Urine, blood, and blood chemical studies were normal. Pelvic diagnosis was bilateral cystic ovaries. Abdominal and pelvic findings at operation were free fluid in pelvis and abdomen; a plastic exudate was noted over the parietal and visceral peritoneum, adnexa, and uterus. The pelvic organs were one conglomerate mass with no possibility of surgical removal. The peritoneal fluid was taken for culture and staining; these were found to be negative. Biopsy of tissue removed from the mass was positive for tuberculosis. The patient was asked to return to the hospital in six weeks for x-ray administration to the pelvis.

Her first series of x-ray was 50 roentgen units on successive days for four treatments. In this series the H.V.L. in copper equaled 1.05 mm. This first series of x-ray was not a sterilizing dose and produced no pelvic improvement. Two months later, following her second series of x-ray treatments which totaled 800 roentgen units her pelvic mass began to disappear rapidly as shown by monthly examinations and she became more comfortable. This patient has a normal pelvis to palpation at the present time, approximately sixteen months following operation.

CASE 3.—E. L., a 35-year-old parous woman was admitted to the hospital complaining of pelvic pain and a draining abdominal sinus which followed an indeterminate pelvic operation three years previously, at another institution. Her abdominal incision had opened and closed several times, draining considerable pus on several occasions before her admission to this hospital. Her menses were normal. Her temperature range was between 99° and 100° F. by mouth. Her hemoglobin upon admission was 54 per cent, and she was given 500 c.c. of citrated blood. Urine and blood chemical studies were normal. Wassermann was negative. Vaginal smears were negative. Smears and cultures from sinus tract showed *Staphlococcus albus*. Mantoux test after forty-eight hours was negative. Chest x-ray was negative. Barium enema was negative for intrinsic organic disease. This was given because of mucopurulent material in the stool; tuberculosis of the large bowel was also being considered. Pelvic examination showed a large mass filling the pelvis which was hard, nodular, and very sensitive. Pelvic findings at operation were a large inflammatory mass with the intestines knotted together by dense adhesions, the visualization of the pelvic organs was impossible. No line of cleavage could be found for the removal of the inflammatory mass. Microscopic examination of a biopsy taken at the time of operation was reported tuberculosis. Two weeks following operation the patient received 100 roentgen units of x-ray daily for three days in which the H.V.L. in copper equaled 1.0 mm. This patient was given another series of deep x-ray treatments with the same dosage four months later. A remarkable subsidence of the pelvic mass was shown at her periodic examinations. At the end of the year the pelvic examination showed an essentially clear pelvis. Interestingly enough, two years after the initial x-ray treatment had been given an abdominal sinus was still draining; this was excised. A progress note made seven months following this excision showed the abdominal wall to be well healed.

CASE 4.—G. J., aged 20 years, was admitted to the hospital on Dec. 5, 1935, complaining of abdominal pain and distention, general malaise, fever, nausea and vomiting, diarrhea, profuse night sweats, extreme toxemia, and a weight loss of twenty pounds since onset of the illness. Her history revealed no tuberculosis in the family. Her menses were normal. She had no leucorrhea. Her general physical examination showed her lungs to be normal. The x-ray plate of her chest showed no significant variations from normal on admission, however, three months later minimal tuberculous infiltration of left apex was reported. The sputum was negative to smear and culture, as was the gastric aspiration. Cultures for the tubercle bacillus were also negative. Her sedimentation test was that of an acute inflammatory process. Guinea pig inoculation was negative. Pelvic examination showed bilateral, fixed, stonelike masses in both fornices. The mass on the right side was about 10 cm. in diameter, while the left-sided mass was indeterminate as to size.

Fifteen days following admission, a laparotomy was performed. Upon opening the peritoneal cavity it was found that the intestines were bound down and involved in bilateral adnexal masses with adhesions involving the visceral and parietal peritoneum. There was a very slight amount of straw-colored, free fluid in the abdominal cavity. The uterus was normal, but was fixed by the inflammatory mass. The pelvic organs were studded with small, white, miliary nodules. It was impossible to do any extensive exploration because of the acuteness of the inflammatory process. Biopsies were taken of the nodules. The abdomen was closed. The microscopic examination of the nodules was reported as tuberculosis. Ten days following the operation it was decided to give the patient x-ray therapy. On three consecutive days the patient was given 100 roentgens, with the H.V.L. in copper equaling 1.0

mm. to the anterior abdomen and pelvis. The patient was discharged from the hospital on Feb. 11, 1936, six weeks after the preliminary series of deep x-ray. At examination before discharge the abdomen was found to be less distended with a definite decrease in the right-sided mass and with the general condition of the patient greatly improved.

The patient was readmitted on March 16, 1936. During the interval in the sanatorium there had been little change in her abdominal symptoms, however, she did have some dull aching in the lower abdomen. On combined abdominal and pelvic examination the hard mass in the right fornix, which was continuous with the abdominal mass on that side, showed little change, however, the left fornix was now relatively free with only slight induration. The patient was given another series of three deep x-ray treatments of 100 roentgens, with H.V.L. in copper equaling 1.0 mm. for six days, every other day to the anterior right abdomen and the alternating days to the anterior left abdomen. She was discharged on April 6 to return in two months.

Patient was readmitted on May 26, 1936. At this time she was definitely improved over the previous admission, had gained five pounds in weight, had good color, her strength was greater, and she seldom had a sensation of fever. Combined abdominal and pelvic examination showed the uterus to be more freely movable. The nodular mass in the right lower quadrant showed no regression, however, the abdominal mass above and continuous with it, was more nodular. The left fornix was clear. There was no evidence of free fluid. In short, the pelvis was freer than before, but the upper abdomen remained the same. Consequently the patient was given another series of three deep x-ray treatments over the anterior abdomen using the same dosage and quality of radiation as used previously. The patient was discharged on June 3, 1936, to return in three months.

The patient was again admitted on Sept. 1, 1936, at which time she had gained eleven pounds in weight since her last discharge. At each previous discharge the patient had gone to a sanatorium and remained in bed, but during the last three months the patient had been gradually increasing her activities, having had no temperature rise except for one occasion. There had been some increase in pulse rate. At this time there was little change in the pelvis or abdomen on combined examination.

The patient returned to the outpatient department for a check-up on Nov. 1, 1936. At this time she gave a history of having had a normal menstrual period on Oct. 10, 1936, with a slight amount of pain. The patient still was continuing to gain weight and strength. The mass formerly present in the right fornix was no longer palpable. The uterus was anterior, of normal size, and freely movable. The left fornix was clear. The nodular mass was still palpated abdominally just below the umbilicus and was the size of a large orange.

On Jan. 12, 1937, the patient was again seen in the outpatient department, feeling very well and having no complaints. She had menstruated twice in November and once in December, scant amounts without pain. Combined abdominal and pelvic examinations showed no masses.

On March 16, May 18, and July 20, 1937, the patient returned to the outpatient department. She was feeling very well and had no complaints. She was having regular menses. No abdominal or pelvic masses were noted. She returned on Nov. 23, 1937; the pelvic was essentially clear with no evidence of pelvic mass and nothing could be felt on abdominal examination. It was decided at this time to give her a sterilizing dose of deep x-ray. The patient was therefore admitted to the hospital and given three treatments of 100 roentgens with the H.V.L. in copper 1.0 mm. to the anterior right abdomen every other day and to the anterior left abdomen on the alternating days.

The patient was discharged Dec. 1, 1937, to return in six months as thought advisable by the sanatorium.

The patient returned to the gynecologic service on Aug. 16, 1938. She had developed some cough and, after checking her pelvis and abdomen, which were negative, it was thought advisable to exclude the chest from any activity. The tuberculosis service considered her chest findings as negative as was the x-ray of the chest. In view of a normal sedimentation rate she was discharged to be x-rayed every six months.

On Dec. 1, 1938, the patient gave a history of having had regular periods for the past few months and it was deemed necessary to give her another series of deep x-ray directed toward castration. She was given three deep x-ray treatments on three consecutive days of 200 roentgens, with H.V.L. in copper equaling 1.05 mm. The application was 100 roentgens to both the anterior and posterior pelvis at each treatment, giving a total of 600 roentgens.

The patient was again seen on February 28, May 16, and October 31, 1939. Up to this time her course had been uneventful with negative chest, abdominal, and pelvic findings. The total weight gain had been 59 pounds.

CASE 5.—F. L., aged 29 years, Indian, a patient on the Tuberculosis Service, with far-advanced pulmonary tuberculosis, was seen by the gynecologic service. Patient was acutely ill and running a temperature up to 101° F. Her complaints were, in part, a sharp pain, occasionally dull and throbbing, low down in the pelvis radiating into the limbs. She also complained of a similar pain on the right side. There was considerable leucorrhea. On pelvic examination this patient had a large, fixed, irregular mass about the size of an orange on the left side which extended somewhat posteriorly into the cul-de-sac. There was also a smaller mass present, on the right side. The uterus was normal and the cervix was clean. The impression was a tuberculosis of the genital organs. Smears were negative for gonoccoci and acid-fast organisms. Cultures gave no information. It was decided to do a diagnostic curettage with a suspension and culture of the endometrial tissues. These proved to be positive for tuberculosis, however, the endometrium on gross examination looked normal and was somewhat scanty. The pathologic report showed chronic cervicitis and early tuberculous endometritis. This patient was given four deep x-ray treatments of 100 roentgens, with H.V.L. in copper equaling 2.4 mm., two to the anterior pelvis and two to the posterior pelvis on alternating days. The patient was discharged to the State Sanatorium to return in six months.

In a telegraphic report from Dr. R. H. Schmidt, Superintendent of the State Sanatorium, dated Aug. 16, 1946, the findings were as follows: Patient has been afebrile dating two weeks following the x-ray therapy, complete relief symptomatically since May, 1946, with a marked regression of the pelvic masses. The right-sided mass measures 1½ cm. in diameter, and no mass is palpable in the left fornix. No menses since May.

CASE 6.—M. R., a 29-year-old, nulliparous patient was admitted to the hospital complaining of a tumor and pain in her right side. The patient's temperature was normal at the time of admission and remained normal throughout her hospital course. Her urine and blood chemical studies were negative. Wassermann was negative. Vaginal smears were negative. X-ray of chest was negative. Pelvic examination revealed a large right-sided tumor which was diagnosed as an ovarian cyst. At operation, large bilateral tubo-ovarian masses were found; both tubes showed a large hydrosalpinx and were studded with small miliary tubercles (see Fig. 4). The serous surface of the uterus

was also studded with miliary tubercles, as was the serosa of the intestine. The ovaries were also involved in the tuberculous process. A bilateral salpingo-oophorectomy and supravaginal hysterectomy was performed. A biopsy was diagnosed tuberculosis. Two weeks following operation the patient received 100 roentgen units of x-ray daily for three days. The H.V.L. in copper equaled 1.0 mm. Three months following the above series of x-ray treatments, 100 roentgen units of x-ray were given daily for four days. The H.V.L. of copper was the same as the previous treatments. The patient returned every two months for examinations for approximately a year following operation. Her pelvis was always essentially negative.

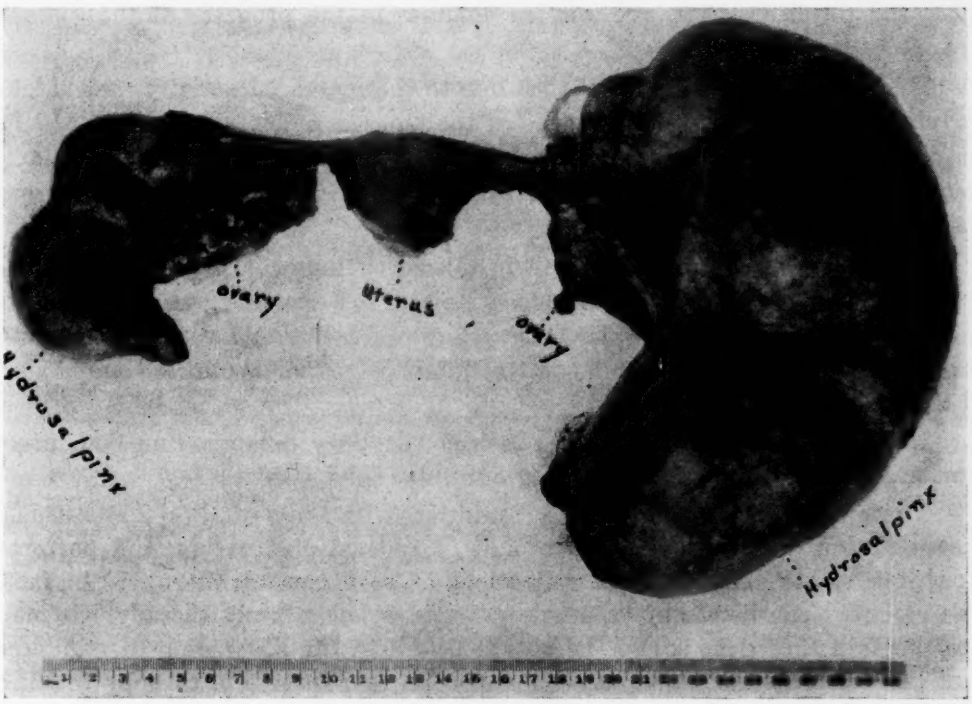

Fig. 4.

Case 7.—E. C., a 42-year-old woman was admitted to the hospital complaining of pain in the left side which was aggravated at the time of the menses. Her menses were normal except for the pain. Urine and blood chemical studies were negative. Wassermann was negative. Vaginal smears were negative. X-ray of the chest was normal. The sedimentation time was slightly active. Pelvic diagnosis was fibromyomata uteri and right ovarian cyst. Findings at operation were that both tubes showed a large bilateral hydrosalpinx; both ovaries were twice normal size and cystic; the uterus was three times normal size but symmetrical. A bilateral salpingo-oophorectomy and supravaginal hysterectomy were done. Pathologic report was tuberculosis of the tubes, ovaries, and uterus. Two weeks following operation the patient received 100 roentgen units of x-ray daily for three days. The H.V.L. in copper equaled 1.0 mm. Two months following the above series of x-ray treatments, 75 roentgen units were given daily for three days. The H.V.L. in copper equaled 1.0 mm. This patient appeared for examinations every two months for more than a year. Her pelvic findings were negative at all times.

Summary and Conclusions

Roentgen-ray therapy, by producing a temporary or permanent castration, tends to conserve the patient's blood and undoubtedly adds to her resistance. This is particularly important in the anemic patient.

Jameson has pointed out that it is a well-recognized clinical observation that tuberculous women are unfavorably affected by their menses. The cough becomes more severe and distressing, the expectoration may be increased, and dyspnea more marked. Examination of the lungs at this time usually shows increased physical signs, and sudden changes in the progress of the disease are likely to occur.

By analogy it seems logical that due to the increased activity and vascular changes in the pelvis at the time of the menses, a deleterious effect would be produced upon the pelvic tuberculosis as is produced in the lung. In fact, temporary or permanent castration by roentgen rays in the pelvic tuberculosis may be a blessing in disguise.

The x-ray dosage as carried out in this series is not large enough to have a profound effect upon the white blood cells, and I cannot agree that it interferes with healing. However, it is a well-known fact that x-rays do stimulate the production of young fibroblasts which is most important in the conversion of tubercles into fibrous tissue.

Roentgen rays are useful in reducing secondary inflammation and infection which is important in the healing of a tuberculous process.

There is no real evidence as substantiated by these studies that fistulas, dissemination of the tuberculous process, intestinal obstruction, and perforation of a viscus are serious complications of roentgen-ray therapy. In fact, I have cured one fistula of tuberculous origin by deep x-ray therapy. It may also be said that deep x-ray therapy is useful in the absorption of exudates and the reduction of secondary inflammation and infection, thereby tending to relieve and prevent intestinal obstruction.

I feel that failures of roentgen-ray therapy as used by the early observers were due to unwarranted dosage with improper spacing. The ideal dosage is one that produces temporary or permanent castration; I tend toward the latter. As Dr. J. M. Wilkie has pointed out, the physiologic age is increased by castration which acts favorably toward the healing of tuberculosis in general. I emphasize the fact that healing of the pelvic disease may favorably effect the healing of this disease elsewhere, and, also, the disease elsewhere may unfavorably effect the progress of the pelvic disease. The more active the tuberculous process, the less favorable will be the prognosis.

In this series it can be stated that roentgen-ray therapy gave excellent cures in most cases, and it must be emphasized that x-ray therapy is an important adjunct following surgery.

The diagnosis of pelvic tuberculosis is usually made at laparotomy. If the pelvic disease can be diagnosed by such procedures as curettage, including suspension and cultures of endometrial tissue, endometrial biopsy, and exami-

nations of vaginal secretions, then pelvic tuberculosis should be treated exclusively by roentgen-ray therapy; however, without positive evidence of tuberculosis this treatment should be condemned.

I wish to thank Dr. James M. Wilkie and Dr. Helen Dickie of the Tuberculosis Service of the University of Wisconsin, for their invaluable assistance and cooperation.

Discussion

DR. HERBERT E. SCHMITZ, Chicago, Ill.—This interesting and scientific study carried on by Dr. Campbell and his associates demonstrates conclusively the value of x-ray therapy in the treatment of pelvic tuberculosis. We should feel deeply grateful to him for bringing these facts before our Society. The literature bears definite proof of long years of neglect of irradiation therapy, due to the gynecologists' training in the surgical management of this disease. That this latter method is faulty is evidenced by an operative mortality rate of 7 to 8 per cent and an occurrence of postoperative fistulas in from 5 to 10 per cent. These figures are based on numerous case reports found in the literature.

In Dr. Campbell's animal study he had few complications arising as a result of x-ray therapy. In all 20 dogs treated in this manner the disease remained limited to the pelvis, and a direct effect upon the absorption of the exudate and reduction of the secondary inflammation was observed. In some cases as many as eight operations were performed on the animal, and in only one case did a fistula form.

Although Dr. Campbell believes an amenorrheic dose of x-ray to be most satisfactory, his Case IV had "negative findings" before the dosage had brought about this effect. In Cases VI and VII a bilateral oophorectomy was performed as part of the surgical therapy, and x-ray therapy could have acted only in clearing up or preventing residual granulations. That this is the action of x-ray therapy on pelvic tuberculosis is the general opinion of the radiologists, and the present dosage advocated by the majority of radiologists is a 5 to 50 per cent E.S.D.* According to McIntosh, the average dose advocated by numerous workers seems to be 10 to 15 per cent E.S.D.,* repeated weekly two to four times, and in several cycles at monthly or longer intervals. This dosage has recently been shown by Glenn of Duke University to elevate the phagocytic indices of rabbits. He found that if 100 roentgens (air) delivered at 140 kilovolts were given to rabbits the phagocytic titer between the first and fourth day showed a significant rise. Higher dosage or 200 kilovolts was only half as effective. He could not conclude as to whether or not the effect of irradiation is on the antibody producing mechanism, on the leucocytes, or on the plasma, or is a result of denaturation of local tissue proteins.

Our technique has varied little since it was first published by Henry Schmitz in 1925. Using 140 kilovolts at 50 cm. focal skin distance 150 V (air) are given to an anterior field. The size of the field is governed by the extent of the disease. This dosage is repeated to a posterior field three days later and this cycle repeated at weekly intervals until four such exposures have been given. A repetition of this dose is administered only if the absorption ceases and there is residual disease. Castration is not our primary object. If Dr. Campbell were to treat some of his animals with bilateral oophorectomy alone he would answer for us the role of castration in the treatment of pelvic tuberculosis.

In summarizing the use of x-ray in these cases I would suggest its use in tuberculosis of the endometrium with no symptoms referable to the tubes. I am acquainted with the high incidence of tubal involvement.

In frankly diseased tubes I would suggest surgical removal of the diseased adnexa followed by x-ray to prevent recurrent granulations.

In advanced cases I favor surgical procedures to confirm the diagnosis and to remove fluid and necrotic tissue. X-ray therapy should be administered as soon as the patient's conditions permits her transportation to the therapy department. Dosages as advocated should provoke very slight reaction if any.

*Erythema skin distance.

DR. W. WAYNE BABCOCK, Philadelphia, Pa.—This paper brings to my mind experimental work that was taking place in 1890. At that time doctors were journeying to Dr. Koch's laboratory in Germany where he injected experimental animals with tubercle bacilli, produced a localized tuberculosis, and then injected tuberculin, when the lesions melted down, discharged, and the animals promptly recovered. The visiting doctors returned home and indiscriminately used the treatment on their tuberculous patients. Large tuberculous pulmonary consolidations melted down, obstructed the bronchi, with suffocation; or other fatal results followed the therapeutic use of tuberculin and it was largely abandoned. Having seen in New York some of the early dramatic results in patients with lupus, I was led to use a mixed bovine and human tuberculin for surgical tuberculosis, and some of the results obtained have been spectacular. A recent example was in a man referred for the operative removal of a rapidly enlarging and very much indurated breast, diagnosed as sarcomatous. From the injection of ¼ minim of the mixed tuberculins there was a marked reaction. The breast became very red, hot and swollen, and soon softened, so that the liquefied contents could be evacuated through a small incision. Several additional injections were given, and at the end of two months the breast appeared normal. Similar results have been obtained with tuberculous collections in the abdomen and pelvis. One woman with pelvic tuberculosis, rectovaginal fistula and involvement of the anterior abdominal wall had had eleven unsuccessful operations during a period of twelve years. After a series of tuberculin injections the fistula was closed and the patient has remained well for nine years. From these and other apparent cures I feel that tuberculin should be reconsidered. However, patients treated should be selected carefully and be free from any extensive disease of the lungs or central nervous system. After testing, massive doses should be used, with intervals of rest to carry the patient well over the negative phase. As the tissues often are unable to absorb the liquefied tuberculous material, evacuation by aspiration or incision is often necessary.

DR. JAMES A. CORSCADEN, New York, N. Y.—I would like to extend this discussion to the treatment of fibroids complicated by pelvic inflammatory disease and reduce the mortality from about 8 per cent in such cases to zero. I am speaking of the pyogenic infections as well as tuberculosis. We have a series of some 20 cases of fibromyoma complicated by pelvic inflammatory disease so treated. In 12 of these, operations had been attempted and abandoned because of technical difficulties. In all of them the abnormal bleeding stopped in 75 per cent of them, subjective symptoms (pain) subsided, and in all the mass diminished in size. These principles can be applied to cases of either tuberculosis or pyogenic infections. The essential factor is the proper dosage.

THE BACKGROUND OF CANCER OF THE CORPUS*

JAMES A. CORSCADEN, M.D., AND S. B. GUSBERG, M.D., NEW YORK, N. Y.

(From the Sloane Hospital for Women and the Department of Obstetrics and Gynecology, College of Physicians and Surgeons, Columbia University)

OF THE many avenues through which the cancer problem may be attacked, that through the study of the individual in whom the cancer is to grow, is attracting increasing interest. From the practical standpoint, in the present state of our knowledge, the principal means by which cure rates can be raised is by decreasing the time lag between the onset of the disease and the application of therapy. The ability to identify the individual who is destined to contract cancer would enable us to bring her under close scrutiny or even institute prophylactic measures; in the case of the corpus uteri, prophylactic hysterectomy.

This hope is based on the idea that certain individuals are possessed of genes which determine characters which make them more liable to the development of cancer than their fellows, an idea which is acceptable to those who believe that cancer is not an acquired disease but is a condition resulting from the breaking down, distortion, or perversion of the laws which control normal cell growth. The normal cell is created, grows, functions, and dies. During its growth and while it remains active, it lives with its neighboring cells in a state of perfect balance so that none encroaches upon another. What maintains this equilibrium for so many decades is unknown but, like all biological processes, goes through its cycle and finally in these cases breaks down, allowing one cell or group of cells to grow lawlessly and encroach upon its neighbors, finally to become a definite cancer. Some individuals possess genes which determine controls so rigid that the normal balance is maintained to an advanced age. In others the control is so feeble that it breaks down early either spontaneously or under some carcinogenic influence.

In attempting to discover those individuals who are especially prone to contract cancer we may study their (1) heredity, (2) the coexistence of observable characters with the cancer tendency, (3) the pattern of behavior, and (4) those environmental factors which may instigate the cancerous process.

Heredity, from the experimental standpoint and from a study of humans, seems definitely to be a factor in the tendency to grow cancer.[1-4] But for practical purposes the study of heredity in an individual is rarely possible because of our reckless breeding customs and the lack of records of the occurrence of disease in and the causes of death of our ancestors.

A linkage between an observed character and one which determined a cancer tendency has been observed by Strong[5] who found that among brown

*Read at the Fifty-Seventh Annual Meeting of the American Association of Obstetricians, Gynecologists, and Abdominal Surgeons, Hot Springs, Va., Sept. 5 to 7, 1946.

mice those who by a mutation were colored black were significantly prone to develop fibrosarcoma at the site of injection of methyl cholanthrene. The chromosomes carrying the gene which determined black hair color also carried a gene which determined the tendency to grow the fibrosarcoma. Both characters followed Mendelian laws in successive generations. In humans, many inherited characters have been observed and some 200 popularly described,[6] and a beginning has been made in the attempt to correlate these types with the tendency to contract cancer.[7-10] These observations are very suggestive and should stimulate a more intensive study of these factors.

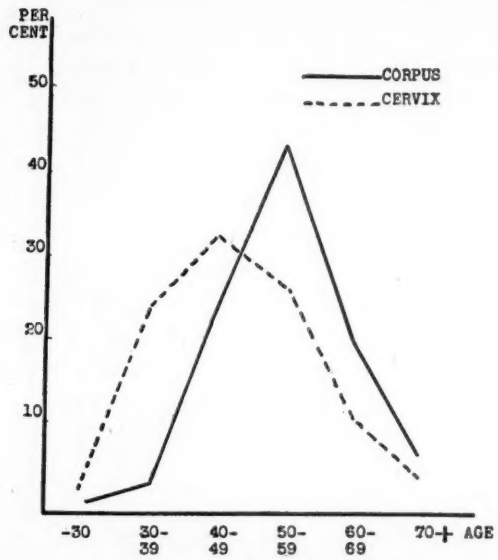

Fig. 1.—Percentage distribution of corpus and cervix cases falling within the different ten-year age groupings.

Our interest in this matter arose in the Sloane Tumor Clinic following a remark by Dr. Julius Gray that the women suffering from cancer of the corpus seemed to be much larger and heavier than those suffering from cancer of the cervix. Observations on age, race, weight, marital status, parity, and economic condition were routinely recorded on the charts. A study of these yielded some apparently significant data which are here presented as a preliminary to a more intensive study of patients who have contracted cancer in the hope that a plan may be outlined which could be used by several clinics in order that conclusions might be reached which would require a much longer time if made from observations in a single clinic.

For controls, the group of cases of cancer of the cervix was taken because it seemed interesting to compare the backgrounds of two malignant conditions in the same organ and because of the difficulty of establishing a norm for the general population in such matters as parity.

Fig. 1 shows the average age of women with carcinoma of the corpus to be 6.6 years greater than those with cervical cancer. This difference is less than is usually given. Study of race showed nothing in particular, except that there

were a proportionate number of Jewish women among those with cancer of the corpus, whereas among 765 cases of cancer of the cervix, there was only one in a Jewish woman.

The weight of the women with cancer of the corpus was significantly greater than that of women suffering from cancer of the cervix. Fig. 2 and Table I show a difference of 18 pounds, a difference nine times as great as the probable error, therefore significant although some difference is accounted for by the different average age. Many of these women not only were heavy but looked big, with heavy round hips and shoulders and small hands and feet.

TABLE I. MEAN WEIGHTS FOR CERVIX AND CORPUS SERIES

	NUMBER	MEAN	+ POSSIBLE ERROR	STANDARD DEVIATION
Cervix	348	140.30	± 0.99	27.40
Corpus	142	158.30	± 1.76	31.20
		difference + P.E.	× P.E.	
		+ 18.00 ± 2.02	8.91	

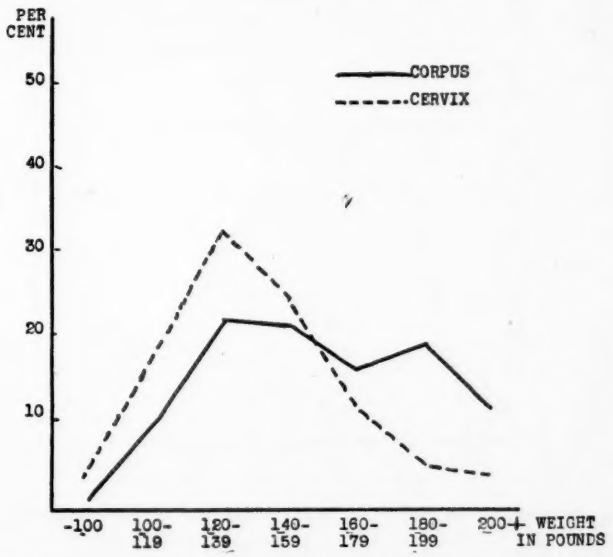

Fig. 2.—Percentage distribution of corpus and cervix cases falling within the different 20-pound weight groupings.

Women with cancer of the corpus did not marry as frequently as those with cancer of the cervix. Fig. 3 and Table II show that 24.8 per cent of 206 women with carcinoma of the corpus were unmarried as against 5.6 per cent of 550 women with cancer of the cervix, a difference of 19.2 per cent ± 2.13, or 9 times the probable error.

TABLE II. DIFFERENCES IN PERCENTAGE OF SINGLE WOMEN IN THE CERVIX AND CORPUS SERIES

	TOTAL NO.	PER CENT	DIFF.	+ P.E.	× P.E.
Cervix	550	5.6	19.2	± 2.13	9.01
Corpus	206	24.8			

TABLE III. DIFFERENCES IN PERCENTAGE OF NULLIPAROUS WOMEN IN THE CERVIX AND CORPUS SERIES

	TOTAL NO.	PER CENT	DIFF.	+ P.E.	× P.E.
Cervix	524	16.6	22.0	± 2.61	8.43
Corpus	192	38.6			

Women with carcinoma of the corpus were more often nulliparous, 38.6 per cent of them having no children as against 16.6 per cent of the women having carcinoma of the cervix, Fig. 4 and Table III, a difference of 22.0 per cent ± 2.61, 8.43 times the probable error. Likewise, the percentage of infertile marriages among women with carcinoma of the corpus is unusually high; 30 of 81 women, or 37 per cent.

The economic status of women with carcinoma of the corpus is also exceptional, 145 out of 308, or 47 per cent, being private patients as against 182 of 765 patients with cancer of the cervix, or 23.8 per cent.

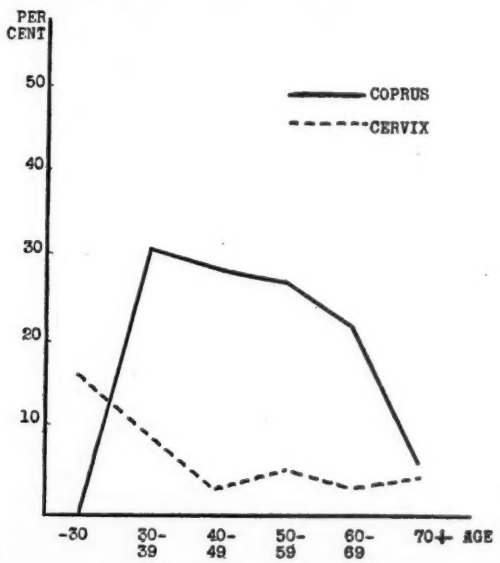

Fig. 3.—Percentage distribution of single women by age groups in the corpus and cervix series.

The menstrual pattern of these patients is also suggestive. Of 10 patients who developed carcinoma of the corpus prior to the menopause, five showed long-standing gross abnormalities of menstruation. Studies of the menopausal pattern in patients who later developed adenocarcinoma of the uterine corpus also revealed deviation from the normal. (a) The age incidence of cessation of menses was distinctly later than the 48-year average usually given—the peak incidence in our group coming in the 52- to 54-year range (Fig. 5). (b) The incidence of excessive and irregular bleeding during the menopause was greater in this studied group than in the general female population. Thirty-two patients, or 39 per cent, of the 82 who contracted the cancer after the menopause suffered from uterine bleeding abnormalities during the climacteric; this is three times the expected incidence of 13 per cent.[11]

Further observation bearing on the question of the nature of the menopause and its relation to subsequent carcinoma was made on 1,100 women who had received a radiotherapeutic menopause for benign causes of bleeding and were followed for an average of 6.7 years.[12] Among them there were observed 15 cases of cancer of the uterus, which was three and one-half times as many

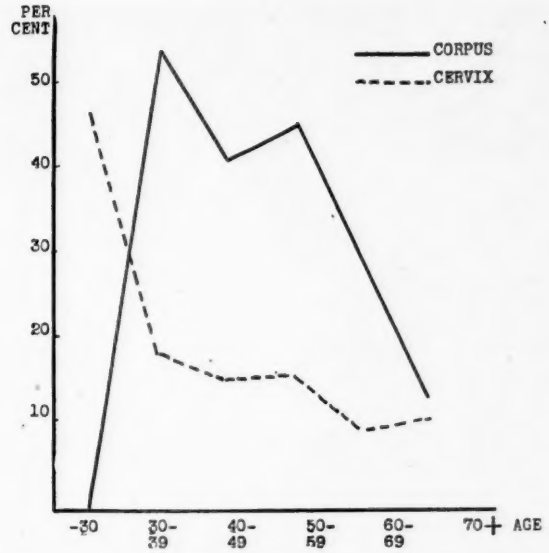

Fig. 4.—Percentage distribution of nulliparous cases by age groups in the corpus and cervix series.

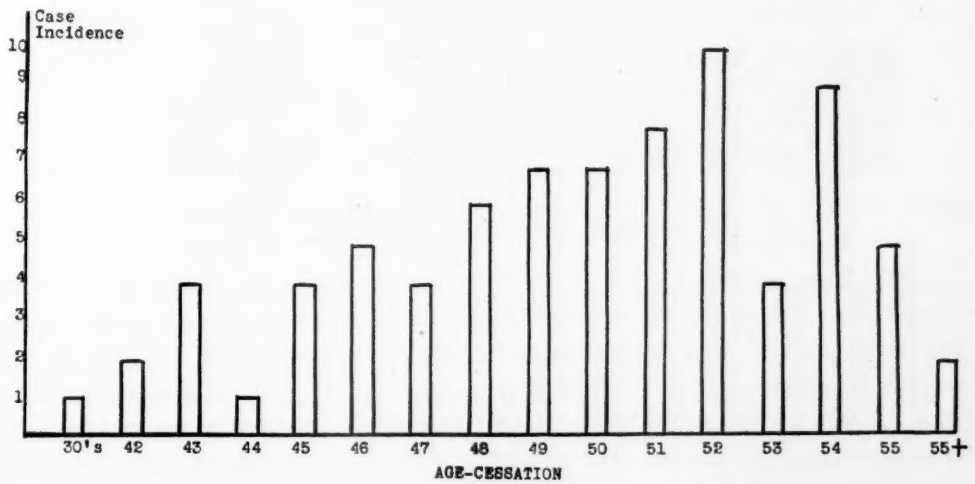

Fig. 5.—Age at menopause in patients who developed carcinoma of the corpus postmenopausally.

as would be expected in a similar sample of the general population. Nine of these were in the corpus and six in the cervix, the number in the cervix being what it should be; those in the corpus being three times the number to be expected. Randall[11] made a similar observation on a group of cases in whom there had been no radiotherapeutic menopause.

The nature of this relationship between a menopause characterized by excessive bleeding and subsequent carcinoma of the corpus and a similar pattern of irregularity preceding cancer occurring before the menopause is not established; speculation concerning this pattern leads naturally to a study of growth stimulating substances involved in the sexual cycle, especially the estrogens.

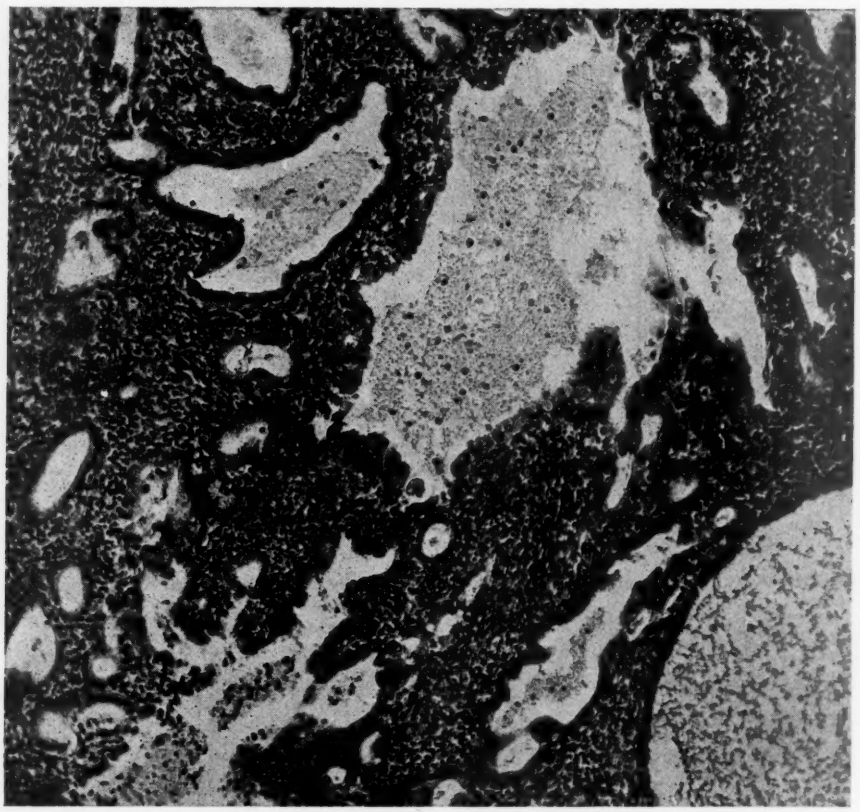

Fig. 6.—Endometrium of a postmenopausal patient after moderate estrogen stimulation, showing hyperplasia and epithelial activity.

We have collected data concerning the relation of unopposed estrogen stimulation and abnormal growth of the human endometrium, which we are now studying and will present later in detail. It is our purpose here to offer several fragments of evidence which suggest to us such a possible relationship. Many investigators have studied the effect of stimulating or inhibiting substances on high cancer strain mice, for example, which apparently possess this proper inherited substrate which makes for cancer susceptibility.

It has been well established that unopposed estrogen stimulation of the human endometrium will result in cystic glandular hyperplasia. We have found 31 per cent of uteri curetted for bleeding during the menopause to harbor hyperplastic endometrium. This condition may be the result of the patient's own endocrine imbalance, or it can be produced by the administration of estrogenic substances. In studying the background of patients who have

developed corpus carcinoma, we do not find constant evidence of hyperplasia of the endometrium, but we have noted findings such as frequency of the bloody menopause, the delayed menopause, and increased incidence of sterility, all of which could be interpreted as evidence of endocrine imbalance; clinical phenomena sometimes associated with absent or infrequent ovulation. Curettage at other stages of the bleeding process in individual cases might raise this percentage of hyperplasia somewhat, for there is, undoubtedly, repeated building up and sloughing off of this tissue.

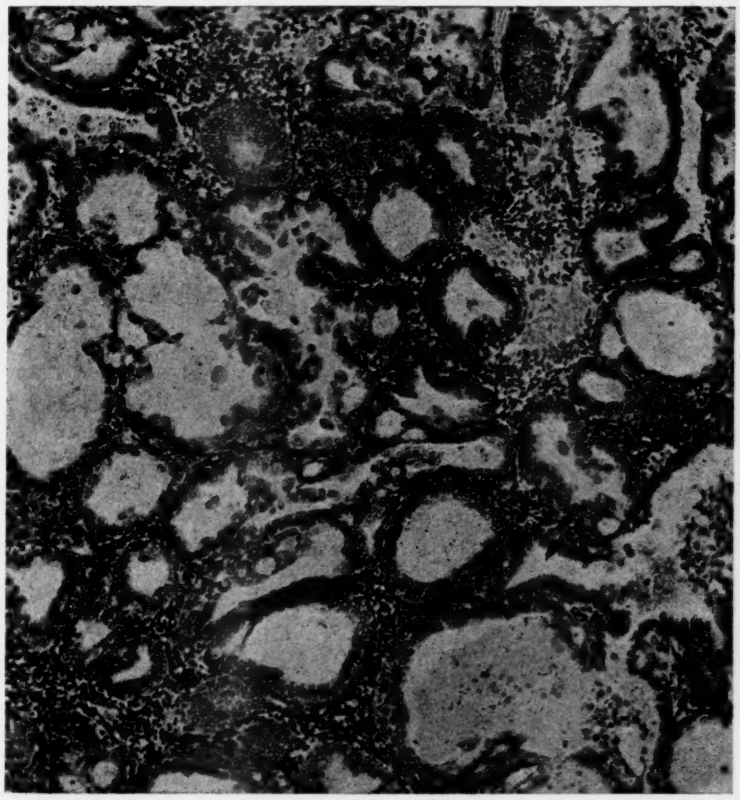

Fig. 7.—Endometrium of a postmenopausal patient after long-continued estrogenic therapy, showing adenocarcinoma.

A natural experiment in abnormal estrogen stimulation of the postmenopausal human uterus is set up in the patient who develops a granulosa-cell (or theca-cell) tumor of the ovary; hyperplasia of the endometrium is a common finding in this condition. It is interesting to note the increasing number of reports[13-21] which stress the relatively high incidence of corpus carcinoma associated with these tumors. This type of evidence is extremely suggestive of an estrogen-cancer relationship.

Another human experiment has been set up by the widespread administration of estrogens to postmenopausal women. We have studied 20 endometria with extreme degrees of hyperplasia produced by long-continued estrogen administration (Fig. 6). For the most part the medication used was stilbestrol,

but this is merely a reflection of its low cost and the ease of its administration rather than the presence of any exceptional qualities. We have not found this response to be related to the quantity of the drug, but rather to the persistent stimulus. We have also studied five patients with corpus carcinoma, appearing after long-continued estrogen administration, whose histories are strongly suggestive of an etiologic relationship (Fig. 7). The histologic pattern of these adenocarcinomas in many instances bears a considerable resemblance to the hyperplastic and metaplastic endometria mentioned above. We also have collected three other corpus carcinomas whose development may have been accelerated by estrogen administration and their histologic pattern possibly modified. These data will be presented in a later communication.

Fig. 8.—Endometrium with marked hyperplasia and metaplastic areas suggesting adenocarcinoma.

The relation of hyperplasia of the endometrium to cancer has been debated for some time[22-27] without arrival at any conclusion. It is true that the gynecologic pathologist frequently sees hyperplastic endometria which suggest a stage in the development of carcinoma; he also sees corpus carcinomas with coexisting endometrial hyperplasia, and he sees hyperplastic endometrium curetted from postmenopausal women who later develop true adenocarcinoma. He will occasionally advise prophylactic hysterectomy for a patient with marked

endometrial hyperplasia, though he cannot label the curettings adenocarcinoma (Fig. 8). Similarly in the group of hyperplastic endometria produced by estrogens, there were none which one could call carcinoma, but there were some which produced such an uncomfortable suggestion of cancer in the minds of the experienced pathologists who studied them, that they advised removal of the uterus as a prophylactic measure.

All these suggestive bits of evidence have brought us to the belief that unopposed estrogenic stimulation, either endogenous or exogenous, may be one of the carcinogenic factors for the uterus if the genetic substrate is such as to create a properly cancer susceptible tissue. Whether the general constitution, the apparently unusual marital and childbearing experience can be connected with this evidence of estrogen activity is a matter for interesting speculation. The data are too meager for any definite conclusions, but are suggestive enough to stimulate further study along these lines.

Conclusions

From these few observations it would appear that an unmarried woman and if married, childless, who was overweight and in comfortable circumstances is a likely candidate for a cancer of the corpus at some time in her life. If her menopause is characterized by excessive bleeding, the chances of her contracting carcinoma are still greater.

We have briefly mentioned several fragments of evidence suggesting abnormal estrogenic stimulation as one of the growth-stimulating factors.

The evidence presented suggests that women destined to have carcinoma of the corpus are measurably different from other women. More precise measurements of these differences should be made.

We wish gratefully to acknowledge the assistance of Dr. C. W. Dupertuis in the statistical analysis of these data.

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Discussion

DR. W. A. COVENTRY, Duluth, Minn.—Climacteric or postmenopausal uterine bleeding can be due to too prolonged and continuous treatment with estrogenic substances, which produce an endometrial hyperplasia, as suggested by Taylor. This is becoming a common observation, especially when a curettage is performed for "spotting" in the 40 to 60 age group, and undoubtedly calls for a more rational approach to the administration of estrogenic substances.

The incidence of uterine bleeding at 40 years of age or over is certainly increasing markedly and, of course, has made it imperative to do more uterine curettements. However, I do not believe that there has been an increase in the incidence of malignancy of the fundus of the uterus. The consensus of most authors is that carcinoma of the fundus is far greater after the menopause than before, and that there is no correlation between the increased incidence of fibroids and the presence of malignancy; in fact, the combination of carcinoma and fibroids is quite rare.

In a review of 128 cases in Duluth over the past ten years, there were only three cases of carcinoma of the fundus of the uterus coexisting with fibroids, or an incidence of 2.9 per cent. Our pathologists report all of the cases of carcinoma of the fundus as Grade I (Broder's), which corresponds with the findings in the literature.

Opinions vary as to the proper treatment of these cases. From my experience, if there is continued spotting from the uterus, especially in a menopausal or postmenopausal patient, the correct treatment would seem to be a careful systematic curettage; if no malignancy is found in the tissue from the fundus, then I would de-estrogenize the patient by discontinuing estrogenic treatment. If, however, malignancy is found, I would give first a course of deep x-ray therapy, followed by a radical hysterectomy (removal of the entire uterus, plus the tubes and ovaries). In this way at least 99 per cent of the cases will be cured.

DR. CLYDE L. RANDALL, Buffalo, N. Y.: At the Buffalo General Hospital we have taken from the files the last 200 consecutive cases of cervical carcinomas and a like number of adenocarcinomas of the fundus and have charted the differences in their ages, weights, marital status, and parity.

Our observations substantiate those just reported by Dr. Corscaden, who noted that 24.8 per cent of his patients with carcinoma of the fundus and 5.6 per cent of women developing carcinoma of the cervix were single. Likewise we found that 18.7 per cent of our women with adenocarcinoma as compared with only 2.4 per cent of patients with cervical malignancy had never married. Similarly, Dr. Corscaden found 38.6 per cent of married women developing adenocarcinoma had no children, whereas only 16.6 per cent of women with carcinoma of the cervix had been nulliparous. We found that 28.2 per cent of married women developing adenocarcinoma had been childless, while only 13.9 per cent of patients with cervical carcinoma had no children. The number of children per parous individual was not reported by Dr. Corscaden, and we found no significant differences in that regard. The married women developing adenocarcinoma had borne an average of 1.66 children, whereas the women with carcinoma of the cervix had an average of 2.29 children.

I feel that the factors predisposing the individual woman to adenocarcinoma of the uterus must be recognized in her medical history and in the characteristics of her physique. It is important that we recognize the woman so predisposed, particularly if so-called routine pelvic examinations are to be employed as a cancer prevention measure. While local, visible changes may arouse our suspicion of cervical malignancy, little can be found on inspection or palpation to increase the examiner's suspicion of endometrial carcinoma. While carcinoma arising in the endometrium occurs less frequently than squamous-cell carcinoma of the cervix, the curability of fundal carcinoma assures it greater consideration than the mere frequency of the lesion would otherwise justify.

Granting the possible significance of certain characteristics of physique, I am personally convinced that endocrine dysfunctions associated with functional bleeding or a late menopause provide a practical basis for recognition of the woman predisposed to the development of adenocarcinoma of the uterus.

We have previously reported that over 35 per cent of women ultimately developing carcinoma of the fundus continued to menstruate past their fiftieth year. In comparison, among a group of women failing to develop uterine malignancy over a period of 15 postmenopausal years, 92 per cent had experienced cessation of their periods before their forty-ninth year. If the unopposed action of estrogen upon the endometrium results in an increased incidence of adenocarcinoma, it would seem logical to expect an increased incidence of this neoplasm within a group of women continuing to menstruate (and continuing their opportunity for ovarian dysfunction) several years longer than the average.

Occasionally we hear the suggestion that irradiation, when employed for the treatment of benign causes of bleeding, may bring about changes in the uterus that predispose that organ to the development of adenocarcinoma. The literature suggests that while the use of radium or x-ray may not prevent the subsequent development of endometrial malignancy, the postradiation changes in no way predispose the uterus to the development of adenocarcinoma. We, therefore, feel that a castration dose of irradiation is probably advisable whenever a diagnostic curettage is indicated for functional bleeding during the climacteric years. Moreover, when vaginal repair or a pelvic laparotomy is indicated for a woman past the childbearing age, in choosing the operative procedure it should be remembered that total hysterectomy would prevent the subsequent development of either cervical malignancy or adenocarcinoma in the fundus.

In the pathogenesis of endometrial carcinoma, an unopposed estrogen effect is not mandatory, for adenocarcinoma frequently develops before the menopause in the presence of a corpus luteum. There seems little evidence that the relatively transitory progesterone effect exerts either a positive or negative influence upon the development of adenocarcinoma in the uterus. On the other hand, as Dr. Corscaden has emphasized, evidence of prolonged estrogen stimulation occurs frequently in women developing adenocarcinoma of the uterus. Few believe that endometrial hyperplasia is a necessary precursor of adenocarcinoma, but the incidence of fundal carcinoma among women with a history suggesting prolonged estrogen effect and endometrial proliferation cannot be denied.

The development of endometrial malignancy in the uterus of a woman who has previously had both ovaries removed or who had been castrated by adequate doses of irradiation should not be offered as evidence that adenocarcinoma can develop in a uterus not previously primed by estrogen, *unless* the patient's vaginal membrane suggests the atrophic changes expected when estrogen deprivation persists over a period of time.

We have published statistics indicating that whenever postmenopausal bleeding occurs, the woman with a history of menorrhagia during her climacteric years has three and one-half times greater chance of having developed an adenocarcinoma of the fundus than does the woman who experienced no increased bleeding prior to cessation of her periods. It will be recalled that Dr. Corscaden's data substantiate that figure. I believe there is a fundamental principle evidenced in the observation that adenocarcinoma does *not* develop in the uterus while a woman is experiencing hot flushes, particularly if on examination she shows atrophic changes and no evidence of estrogen effect on the endometrial and vaginal membranes. Conversely, a woman experiencing functional menorrhagia or metrorrhagia at the

menopause, particularly a woman with clinical evidence of persisting estrogen effect in her postmenopausal years, should be regarded as predisposed to the development of adenocarcinoma in her uterus.

DR. EMIL NOVAK, Baltimore, Md.—Although we have long been in the habit of speaking of cervical inflammatory lesions as predisposing to the development of cervical cancer, there has been little said as to factors which might predispose toward carcinoma of the uterine body. Dr. Corscaden's remarks on the significance of an unusually late menopause are in line with the observations of Hobbes and Crossen, and my own experience makes me feel that this factor does have a significance. Another which he mentioned, and which he supported staistically in his recent paper on the subject, is that represented by a history of functional menopausal bleeding, since women who have been treated for such a disorder show a later incidence of carcinoma three and one-half times as great as others.

A third factor which has impressed me as of probable predisposing importance is the exposure of the postmenopausal endometrium to persistent estrogenic stimulation, in the absence of what may possibly be the protective influence of progesterone. That such postmenopausal production of estrogen occurs not infrequently is well known, and we have found postmenopausal endometrial hyperplasia not infrequently in association with adenocarcinoma. There would seem to be an obvious relationship between all three of the factors which have been mentioned.

The largest number of adenocarcinoma cases in Dr. Corscaden's cases were between the ages of 50 to 55 years, and a similar incidence is noted in studies by others. The significance of this, in relation to the factors previously mentioned, is tempered by the fact that mistakes in pathologic diagnosis are more frequent at this age period than at others, since at this time especially we are likely to encounter various degrees of proliferative or adenomatous hyperplasia which are easily mistaken for adenocarcinoma, although they are clinically benign. For example, several of the slides shown by Dr. Corscaden as instances of adenocarcinoma impress me as belonging to this pseudomalignant group, and not to be malignant.

The differentiation requires much pathologic experience, and in some cases must be made almost empirically by the trained microscopist. I have followed many of these cases clinically after conservative treatment, including curettage and radiotherapeutic induction of the menopause, and cancer has not developed. Furthermore, in a good many cases in which the uterus had been removed, further study showed no evidence of cancer. On the other hand, there is a small residue of cases, in which the doubt is very real, and in which pathologists will disagree, and in these the treatment should be that of carcinoma. From what has been said it is easy to understand how cancer statistics can be vitiated by the inclusion of cases in which the lesions are histologically pseudomalignant but really clinically benign.

DR. FRANK R. SMITH, New York, N. Y.—I would like to ask Dr. Corscaden whether, in this series of patients presented a preliminary curettage had been done before using stilbestrol. I think it is important that from these patients we should have at least a biopsy by Dr. Novak's method or by curettage before stilbestrol is administered to women of menopausal age.

I was interested that Dr. Corscaden noted 15 cases in 900 patients treated with irradiation that later developed carcinoma of the body of the uterus. During the years 1924 to 1934 at Memorial Hospital we had about 1,000 patients treated with small doses of radium for endocrine imbalance. Only four of that group have later developed carcinoma. We have had about 21 patients come to the hospital in later years who were treated at other hospitals during that period but who were not in this original group of 1,000. It is perfectly true that many of our patients might have developed carcinoma and gone to other hospitals. But in that case there is usually a letter requesting information which is filed with the record.

DR. ROBERT SEIBELS, Columbia, S. C.—My discussion will not be confined to the material presented. However, the promptness with which diagnosis and definitive treatment

are accomplished is bound to be reflected in the results achieved in the treatment of carcinoma either of the fundus or the cervix. I would like to review briefly the findings in a case of carcinoma of the cervix in which the diagnosis was primarily made from stained smears of the vaginal secretions. This 39-year-old patient came in for a routine physical examination presenting no symptoms suggestive of malignant change or, indeed, of ill health. The spread was made from vaginal secretions as a purely routine step comparable with the ordinary laboratory tests on urine and blood.

The photomicrographs shown tell the story. In the first one, there were areas of normal vaginal cells with an increase in the leucocytes. In the second is shown a single irregularly shaped cell with a tremendous nucleus.

In the third is shown a group of atypical basal type cells and another group of cells which are distinctly of cancerous appearance with irregularly shaped nuclei, taking stain in various densities and with a nuclear pattern quite typical of epidermoid carcinoma.

Based on these appearances, a biopsy was taken and the first cuttings from the block were compatible with the report of normal cervical tissue.

The next slide shows typical invasion of squamous malignant epithelium and on comparison with the stained smear we find exactly the same type of cells and cellular arrangement.

The sections from the operative specimen continued to show squamous-cell carcinoma of the cervix, Grade II. Here then is a case of early noninvasive carcinoma of the cervix primarily diagnosed by the stained smear and without its routine use it would have been completely overlooked.

DR. JAMES A. CORSCADEN, New York, N. Y. (Closing).—None of these patients in whom stilbestrol has produced a hyperplasia had received their stilbestrol from us. I do not believe that any of them had had a curettage. Apropos of the question of the merits of supravaginal and complete hysterectomy, 8 per cent of our cancer of the cervix lay in stumps following supravaginal hysterectomy. Four per cent is the figure given over the country in general. I believe that we should set an ideal and not teach that the best operation is one based on the capacity of the casual surgeon.

PITUITARY EXTRACT IN UTERINE INERTIA: IS IT JUSTIFIABLE?*

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THE procedures employed in the management of uterine inertia are, in the main, rather well standardized. In secondary inertia, the administration of morphine and intravenous fluids to provide a period of rest and promote hydration has proved widely satisfactory, and is usually followed in a few hours by a return of normal, effectual contractions. In primary uterine inertia, time and patience, repeated reassurance of the patient, and stimulation with enemas from time to time will likewise bring most cases to a happy conclusion. Occasionally, however, cases of primary uterine inertia may prove so refractory to treatment that the question arises as to the desirability of using a really effectual uterine stimulant such as pituitary extract; and ever since that agent was first introduced, some forty years ago, the problem of the justification of employing it in such cases keeps recurring.

The dangers of pituitary extract in the first and second stages of labor in the form of uterine rupture and fetal asphyxia have been repeatedly and vehemently emphasized and, in the opinion of many authorities, are so menacing that this agent should never be used before the birth of the baby. On the other hand, there is ample evidence that a real need for the oxytocic effects of pituitary extract exists if its action could be but safeguarded. Witness, for instance, the many efforts which have been made to moderate the effect of this hormone. Hofbauer's nasal pituitrin represented one such attempt, as did also thymophysin, the various preparations of pituitrin in oil and, more recently, Dieckmann's pitsulfonate. Within the past few months, moreover, Duncan Reid has reported some 1,500 cases from the Boston Lying-In Hospital in which small doses of regular pituitary extract or pitocin were used in the treatment of first- and second-stage uterine inertia with gratifying results.

Our own experience with pituitary extract in the treatment of uterine inertia began in 1926 with Hofbauer and Hoerner's introduction of nasal pituitrin. This was used extensively in our clinic for a ten-year period ending in 1935, but with results which were far from consistent. In some cases the effects were highly satisfactory, in others no action at all could be detected—depending apparently on the ability of the inferior turbinate bones to absorb the hormone. But we put up with these undependable results in the complacent belief that, in any event, it was safe. However, when in our own city, two cases were brought to our attention of ruptured uterus following intranasal pituitrin, we were rudely disillusioned about its safety and abandoned the procedure. Between 1935 and 1940, inclusive, no pituitary extract was employed before the

*Read at the Fifty-Seventh Annual Meeting of the American Association of Obstetricians, Gynecologists, and Abdominal Surgeons, Hot Springs, Va., Sept. 5 to 7, 1946.

birth of the baby. During these five years, we repeatedly felt the need for a reliable uterine stimulant, especially in the first stage inertia, and were particularly disturbed by one maternal death in which uterine inertia played a major role—a case in which prolonged, stubborn inertia, exhaustion, intrapartum infection, Dührssen's incisions, and a difficult midforceps produced a fatal degree of shock. And we can recall a few similar cases of extreme inertia in that period in which the mother did not pay the death toll, but escaped only by a narrow margin.

Being impressed, therefore, not only by the frequency of primary uterine inertia, but by its grave potentialities, we began on Jan. 1, 1941, to treat carefully selected cases of uterine inertia with minute, intramuscular doses of pituitary extract. During the first two years of the program, the initial dosage was limited to 1 minim, during the last three years to ½ minim. Injections are repeated every thirty minutes until satisfactory pains ensue. If no effect whatsoever on the quality of the contractions is observed, the dose may be increased, but this was never allowed to exceed 2 minims. Recently, the upper limit for a single dose has been reduced to 1 minim. The number of injections ranged from one to as many as 35 in a few cases; the average was perhaps three or four. In the great majority of the cases this therapy was carried out in the first stage of labor. Further details of this experience will be published shortly by Dr. Louis M. Hellman of our Department in a more comprehensive study than can be presented in the time limit for this paper.

TABLE I. INCIDENCE OF PITUITRIN STIMULATION, 1941 TO 1945

	CASES	PITUITRIN	PER CENT
Total	8679	463	5.3
Ward patients	6680	233	3.5
Private patients	1999	230	11.5

As may be seen in Table I, pituitary extract was used in 463 cases with an over-all incidence of 5.3 per cent. When our total cases, however, are divided into ward and private patient groups, a glaring discrepancy appears, namely, a three times greater incidence of pituitrin stimulation in private patients than in our ward clientele. This means only one thing, namely, that some of our visiting obstetricians are employing pituitary extract not infrequently for very minor degrees of uterine inertia—cases which patience and time would probably have brought to a satisfactory outcome without oxytocic stimulation. Although there was not a single fetal death in the 230 private cases (except for a fetal monster carried several weeks dead in utero), this practice of employing pituitary extract in virtually normal labor is reprehensible. At the very outset of our study, then, we are confronted with one of the great drawbacks to countenancing any use of this agent before the birth of the baby, namely, its inevitable abuse. Certainly, our experience, as shown in Table I, would indicate that just as soon as any group of obstetric specialists in a community begin to employ pituitary extract before the birth of the baby—be they ever so careful to restrict its use to rigorously selected cases of true inertia—the unnecessary administration of this

agent by less patient practitioners increases. This circumstance is certainly a heavy charge on the debit side of the pituitary ledger.

This series of private patients will appear again in our statistics when the dangers of pituitary extract are analyzed, and rightly so, because all these 230 women were exposed to its hazard. However, since most of them did not, in all probability, represent valid examples of uterine inertia, this group is of little help in answering the important question: what benefits may be expected from pituitary extract in true uterine inertia? For this purpose it is necessary to concentrate on our 233 ward cases, practically all of which were examples of real, often severe, inertia. We define uterine inertia as follows: in the first stage, sluggishness of uterine contractions (after true labor has begun) of such a degree that (1) the cervix shows no change over an eight-hour period, and (2) the uterine wall is easily indentable at the acme of each pain; in the second stage, sluggishness of uterine contractions of such a degree that the head neither rotates nor descends over a two-hour period with a uterine wall which is easily indentable at the acme of each pain. Uterine inertia and prolonged labor, let it be emphasized, are not synonymous, because prolonged labor may be entirely normal and physiologic, provided that steady, if slow, progress is made. Uterine inertia, on the other hand, is complete, prolonged absence of progress in the presence of weak contractions.

TABLE II. DURATION OF LABOR AND INCIDENCE OF INTRAPARTUM INFECTION IN PITUITRIN CASES, WARD AND PRIVATE

WARD CASES			PRIVATE CASES		
		Duration of Labor			
Under 24 hours	108		Under 24 hours	206	
25 to 30 hours	38		25 to 30 hours	12	
31 to 47 hours	61	55%	31 to 47 hours	9	10%
48 hours and more	26		48 hours and more	3	
	233			230	
		Intrapartum Infection			
Ward cases 58 or 24.9%			Private cases 2 or 0.9%		

A good idea of the general character of these 233 ward cases in which pituitary extract was used may be had from Table II, where it may be seen that over half the labors exceeded twenty-four hours, and in one-fourth were associated with intrapartum infection. In 87 cases, or 37 per cent, the duration of labor exceeded thirty hours, and in 26, or 11 per cent, extended over more than forty-eight hours. As a rule, pituitrin was not started until eighteen to twenty-four hours of labor had elapsed with weak pains and a stationary cervix, and after, of course, all the usual expedients, such as enemas, had proved ineffectual. Indeed, the problem of whether or not to use pituitrin in these cases was not so much one of pituitrin vs. further temporizing as it was that of pituitrin vs. some radical method of delivery; and I can give you no more concrete picture of the type of case in which we have used pituitrin on the ward service than by saying that we have employed it, in the main, in the patient who seems to us to be headed, in the next day or two, either for Dührssen's incisions and a difficult midforceps, or extraperitoneal cesarean section.

Having defined uterine inertia, as we regard the term, let us consider what benefits, if any, have accrued during the five-year period in which pituitary extract has been used in the treatment of this condition, as compared with our experience over the preceding five-year period when it was not employed. This is summarized in Table III. It will be noted that there was no diminution in prolonged labor; and from what has been said, this was not to be expected. The majority of these prolonged labors were considered normal, if slow, and pituitary extract was therefore not administered.

TABLE III. BENEFICIAL EFFECTS OF PITUITRIN STIMULATION, WARD CASES ONLY

	PERIOD 1936-40	PERIOD 1941-45
Total deliveries	5529	6680
Pituitrin stimulation	0	233 (3.5%)
Prolonged labor		
Over 24 hours	456 (8.2%)	564 (8.4%)
Over 30 hours	265 (4.8%)	329 (4.9%)
Midforceps	26 (1:212 deliveries)	6 (1:1113 deliveries)
Dührssen's incisions	10 (1:553 deliveries)	5 (1:1360 deliveries)
Total cesarean sections	287 (5.2% or 1:19 deliveries)	254 (3.8% or 1:27 deliveries)
Cesarean section after pituitrin	--	8 (3.4% or 1:29 deliveries)

Perhaps the most notable benefit which we have derived from the use of pituitrin is the dramatic reduction in the incidence of midforceps, from 1 in every 200 deliveries in the nonpituitrin period to 1 in every 1,000 in the pituitrin period. We believe this represents an important saving in fetal life and maternal trauma. The same is likewise true of the 50 per cent reduction in the frequency of Dührssen's incisions. The diminution in the frequency of cesarean section was doubtless the result of many factors, but we feel certain that the use of pituitrin as we have described it played an important role in the lowered incidence. Substantiation is given to this statement by the fact that in this entire series of 233 functionally pathologic labors, only eight cesarean sections were done, that is, in 3.4 per cent of the cases. Had it not been for pituitrin, I am certain that the number of abdominal deliveries would have been several times this figure. Of the eight cesarean sections performed, four were Water's extraperitoneal operations, two were cesarean section-hysterectomies, and two were lower cervical sections with prophylactic penicillin and sulfadiazine.

As shown in Table IV, the uncorrected fetal mortality in the total series, ward and private, was 5.0 per cent. Nine of these 463 patients, however, had suffered fetal death in utero before admission to the hospital, and, if these be excluded from the present analysis, it will be seen that among the patients whose

TABLE IV. FETAL MORTALITY IN PITUITRIN SERIES

	CASES	DEATHS	PER CENT
Total (uncorrected, stillbirths and neonatal deaths)	463	23	5.0
Fetus Alive on Admission			
Total	454	14	3.0
Ward	225	14	6.2
Private	229	0	0.0

babies were alive on admission, the infant loss, from both stillbirths and neonatal deaths, was 3.0 per cent. We consider this a creditable figure. All these 14 deaths occurred in the 225 ward cases, giving a mortality rate of 6.2 per cent for this group. When it is recalled, however, that 58, or one-fourth, of these ward patients suffered from intrapartum infection, and over one-half had labors exceeding twenty-four hours, it seems doubtful if this figure could be greatly improved upon except by wholesale cesarean section. Certainly it would have been much higher had many midforceps been employed in these cases instead of pituitrin stimulation.

TABLE V. CAUSES OF 14 FETAL DEATHS IN PITUITRIN SERIES

CAUSE	CASES
Pituitrin (5 cases of unrecognized or disregarded, borderline disproportion)	8
Maternal rupture of uterus (pituitrin)	1
Forceps trauma	2
Difficult breech extraction—4,340 Gm. infant	1
Encephalocele	1
Maternal eclampsia, prematurity (mother died)	1
	14

The causes of the 14 infant deaths are listed in Table V. Nine of them appeared to be the direct result of pituitrin stimulation. In one, fetal exitus followed rupture of the uterus—a case which will be presented in detail presently. In the other eight, the fetal heart sounds disappeared in the course of the administration of the hormone. It is instructive, from several points of view, to note that in five of these eight cases, unrecognized or disregarded, borderline disproportion was present. In two cases subsequent x-ray pelvimetry showed midpelvic contraction, which had been overlooked clinically. In another, the infant weighed 4,520 grams. In two, although the diagonal conjugates were borderline—11.5 cm.—it was thought that the heads had passed the superior straits and, since both patients had intrapartum infection, it was decided that the cautious administration of ½ minim doses of pituitrin was preferable to extraperitoneal cesarean section. These cases emphasize clearly the high fetal mortality which may be expected if pituitrin stimulation is used in the presence of the slightest degree of disproportion. It may well be argued that this fact itself is an insuperable objection to the use of pituitrin stimulation since, even if one exercises meticulous care and possesses uncanny judgment, a case of borderline disproportion may now and then be overlooked. It is for this reason that we strongly favor x-ray pelvimetry prior to pituitrin stimulation.

There was one maternal death in the pituitrin series in no way associated with the use of the oxytocic. The patient was an eclamptic to whom a single ½ minim dose of pitocin was administered early in a lagging labor; she died post partum of eclampsia.

There was one case of uterine rupture as follows: The patient was a 44-year-old white woman, para viii, weighing 200 pounds, with a pelvis shown to be ample by x-ray pelvimetry. The fetus was in vertex position, with the head at the spines, and was thought to weigh about 4,000 grams. After twelve hours of

labor, the last ten of which were characterized by poor pains and a cervix stationary at 3 cm., a series of nine injections of pituitary extract were given thirty minutes apart, the first three being 1 minim and the last six, 2 minims. Shortly after the last dose was administered, signs of rupture of the uterus developed, and this diagnosis was confirmed at laparotomy, a large rent being present on the left side of the uterus. The 4,250 Gm. child was dead, but the mother made a satisfactory convalescence after hysterectomy.

The case is reported with due humility and with full awareness of our heavy culpability. Although nothing can be said to extenuate this accident, it should be observed that it occurred during the first year of our use of intramuscular pituitrin stimulation, and that today we would not think of giving such a patient this form of medication because she presented one of the most important contraindications to pituitrin stimulation, namely, great multiparity. Evidence of various types shows conclusively that uteri which have carried five or more babies rupture, from all causes, much more readily than the primigravidous uterus, which is relatively immune to this accident.

In addition to this definite instance of uterine rupture, there was one suspected case in which the patient developed a tender mass to the right of the uterus twenty-four hours post partum. Whether this represented a slight rupture or parametritis was uncertain.

Here, then, are the main data on our experience with pituitrin stimulation. Some of you may conclude that the results, particularly the outright case of uterine rupture, should outlaw its use. Others may feel that the benefits achieved outweigh the drawbacks. My own reaction is stated in the following conclusions.

Conclusions

Even if all precautions are exercised, pituitary extract, when given in the first or second stages of labor, will occasionally cause the death of an infant and, less frequently, may result in rupture of a uterus; hence, it is a dangerous drug when given before the birth of the baby. But, looking at the other side of the ledger, uterine inertia also takes its toll in terms of intrapartum infection, exhaustion, difficult forceps, Dührssen's incisions, etc. Which is the lesser evil: pituitary extract or stubborn uterine inertia? Having been brought up to believe that the administration of pituitary extract before the birth of the baby consitutes the most heinous of obstetric sins, but during the past five years having observed its ultra-cautious use in several hundred cases of uterine inertia, I am inclined to believe that the balance lies slightly in favor of pituitary extract—provided, and provided again, that certain rigid rules be observed, as follows:

1. The case must be one of real uterine inertia, primary in character, with labor practically at a standstill and progress nil.

2. The patient must be actually in labor, not in false or prodromal labor. The only valid evidence of true labor is progressive effacement and dilatation of the cervix. Although this process may have come to a standstill, it must have progressed to the extent of 3 or 4 cm. dilatation. One of the commonest mistakes

in obstetrics is to try to "push" labor in patients who are not in labor at all; pituitary extract will only lead to trouble in such cases.

3. There must be no mechanical obstruction to easy delivery as attested by every type of evidence possible, including x-ray study of the pelvis and fetal skull. Unless the latter is done, an occasional instance of midpelvic contraction or of brow presentation may be overlooked.

4. Patients of great parity (paras iv and over, let us say) must not be given pituitary extract because their uteri rupture more readily than those of women in the lower parity brackets.

5. The condition of the fetus must be good, as evidenced by a regular heart beat and absence of meconium-stained liquor amnii. A dead fetus is, of course, no contraindication to pituitary extract.

6. The obstetrician must observe and time the first contraction after the administration of the drug, and given inhalations of ether if it lasts longer than three minutes.

7. *The initial dose must not exceed ½ minim.* This dosage should not be exceeded unless it is clear that no improvement in pains whatsoever ensues. In the latter event, it may then be increased to 1 minim, but under no circumstances should more than 1 minim be given at a time. A period of thirty minutes must intervene between injections.

8. When in doubt as to whether a given case meets the above criteria, do not give pituitary extract.

Discussion

DR. TIFFANY J. WILLIAMS, Charlottesville, Va.—Dr. Eastman makes a distinction between uterine inertia and prolonged labor, but it seems to us that prolonged labor in the absence of obstruction or obvious cervical abnormality is usually associated with varying degrees of uterine inertia. The management of individuals with inertia taxes the ability and patience of the obstetrician, and judicious attempts to stimulate rhythmic uterine contractions are justifiable.

Dr. Eastman does not distinguish in his cases between those with intact and those with ruptured membranes. In those in whom the membranes are intact contractions frequently may be stimulated by artificial rupture of the membranes, and what was formerly an ineffective labor may progress rather promptly to a satisfactory conclusion. If inertia is present after rupture of the membranes, the difficulties are more profound. In instances of inertia, as indeed in all parturient patients, the attendant must assure himself by all available methods of examination including anteroposterior and lateral x-ray measurement films of the pelvis, that no pathologic condition which might interfere with the mechanism of labor exists. Only under those conditions, and with the presenting part well engaged in the pelvis, should one consider the administration of pituitary extracts. The use of pituitrin to stimulate uterine contractions is often a gratifying procedure, but one which is fraught with dangers. We doubt that it should be administered to a patient who is having uterine contractions. The patient to whom it is being administered should be under the constant observation of the physician, and some form of general anesthesia must be immediately available. We personally prefer the intranasal administration, which necessitates the physician's constant presence, so that he can promptly evaluate the uterine response. Under these conditions the chances of prolonged tetanic contraction with rupture are quite remote.

The outlook for patients with uterine inertia and prolonged labor has been appreciably improved in recent years with the present methods of chemotherapy and supportive

treatment. Intravenous glucose with vitamins combats exhaustion and dehydration, and penicillin prophylactically during labor and after rupture of the membranes reduces the frequency and severity of intrauterine infection, and seems to appreciably enhance the chances for survival of the infant.

The necessity for the employment of Dührssen's incisions is really quite frequent, and their use is more often an indication of exhaustion of the attendant rather than exhaustion of the patient. Indeed, rarely if ever is the welfare of the mother or baby enhanced by vigorous and traumatic operative procedures. Usually the prolongation of the labor is safer than its termination by violent vaginal operations. We have employed Dührssen's incisions in our clinic only twice in the past fifteen years.

Dr. Eastman's point regarding the danger of rupture of the uterus in the "*grande*" multipara is well taken and we agree that the use of pituitrin in these individuals is associated with an excessive hazard.

Doubtless, if the course and duration of labor in uterine inertia could be predicted at the onset, many of us would advise abdominal delivery, rather than pursue the slow and tedious course required for vaginal delivery. Murphy has suggested that, by means of the Lorand tocograph, primary uterine inertia may be detected early in labor. It is conceivable that future studies of recordings of uterine tone and contractions may develop to the point where they will significantly affect our decision regarding the method of delivery sufficiently early in labor to safely perform a cesarean section.

I should like to ask Dr. Eastman if he can tell us what is the frequency of inertia in the same patient in subsequent labors? Will subsequent labors also be characterized by inertia? Many times both the patients and ourselves have been too timid to face subsequent labor with its possibility of another inertia and instead we have delivered them by elective section. I have often wondered whether this has been a justifiable decision.

DR. JAMES K. QUIGLEY, Rochester, N. Y.—About 1915, I read one of the earliest papers on the use of pituitary extract in obstetrics. Before ten years had passed I began to regret the publication of that paper, which regret was prompted by several things. The first was the necessity of removing two badly ruptured uteri in a ward service, and I have seen contraction ring dystocia in some cases of my own. I cannot tell you how long ago I abandoned the use of pituitrin before the birth of the baby, but it must be at least fifteen years. In the paper which I read at that time I talked of several precautions that should be observed in the use of pituitary extract during labor, such as full dilatation of the cervix and engagement of the head. Pituitary extract may be used with safety and I have no doubt that Dr. Eastman can use it with safety, but my point today is that I think it is bad teaching, a bad example to have go out from this organization. We have spent years in discouraging the use of pituitrin and we now rarely see it given, even by the general practitioner in our part of the country, and I am aware that after this paper we may encounter some ill effects that follow its use.

DR. GEORGE M. SHIPTON, Pittsfield, Mass.—As Dr. Quigley has said, we have been through a wave of administering pituitrin and are back out of it. I would like to add to Dr. Eastman's remarks a word of explanation. I think this paper is a sort of rebuttal to the recent papers which have been coming out urging the use of pituitrin. Dr. Eastman very carefully analyzed the cases and concluded by saying that in his own experience constantly throughout this experiment the dose of pituitrin had been reduced until it was down to a half minim, and then said, "If there is any doubt, let's not use it." The point of his remarks seemed to be simply to warn us again to get away from the use of pituitrin.

DR. JOHN M. BERGLAND, Baltimore, Md.—I agree with everything Dr. Eastman has said. I was obstetrically brought up by the late Dr. Whitridge Williams in the days before pituitary extract was used. We, of course, used ergot but with very definite rules for the administration of the same. Never until after the delivery of the baby and placenta was it given.

I used the nasal method of giving pituitary extract as advised by Dr. Hofbauer for many years, but I am now using the hypodermic technique which Dr. Eastman has just described. I have never seen a serious case of tetanic contraction of the uterus when the drug is used with care, and I believe firmly that its administration is a distinct help in uterine inertia. I think that uterine inertia is one of the most serious delivery room problems that we have to face and that anything that promises benefit safely should be used to combat it. I agree with Dr. Williams that rupture of the membranes will often help and, of course, the patient should be given as much rest and nutritive fluid as possible. I have never used Dührssen's incisions, but prefer to dilate the cervix manually when it is necessary to do so.

DR. JAMES R. BLOSS, Huntington, W. Va.—I wrote a paper, published more than twenty-five years ago, on "Pituitrin versus Forceps." I was all for pituitrin. I want to agree with Dr. Eastman that the use of pituitrin in carefully selected cases of uterine inertia is not a particularly dangerous procedure. Its use in certain cases, ruling out obstructions, deformities of the pelvis, disproportion, and so on, is often very helpful. With minimum doses, repeated as the effect wears off, proper contractions follow. I believe that you get a synchronization of the uterine contractions without a physiologically explosive effort in cases which are carefully chosen. I did home obstetrics for many years and used much pituitrin. I have never seen a ruptured uterus following its use. I have noted some contraction rings. Five minims of adrenalin hypodermically will relieve contraction ring in a very few moments. Also the careful and intelligent use of chloroform will stop these tetanic contractions from pituitrin almost instantly.

I agree thoroughly that there should be an adequately trained obstetrician. Some persons may have five or ten years' training, some may do obstetrics over a period of twenty years, and yet not have judgment enough to use anything intelligently. I second Dr. Eastman's plea for the judicious use of pituitrin in carefully selected cases.

DR. R. L. DENORMANDIE, Boston, Mass.—I find myself in almost complete agreement with Dr. Eastman. I have never failed to use pituitrin in carefully selected cases, never starting with more than one minim. I never give another unless I have an anesthetist near by to give ether should the patient's uterus go into tetanic contractions. I stopped using it for a while because of the tetanic contractions, but have come back to its use.

I do not hesitate to use it in multiparas of the type that Dr. Eastman refers to, provided I know by previous examination that there is not a cicatrix in the cervix or a bad bilateral tear.

DR. J. BAY JACOBS, Washington, D. C.—This paper seems to center around pituitrin, and the emphasis seems to be on pituitrin rather than on primary or secondary inertia. I am in accord with the essayist and the discussants relative to the dangers of pituitrin, but I believe we have overlooked one important factor in the treatment of inertia, and that is rest. Very often a tired woman needs rest and then her uterine contractions will be of a good character. We must differentiate also in cases of inertia, as to whether it is primary or secondary. In primary inertia uterine contractions may not be very forceful, but quite regular; even though the cervix is not dilating, the woman appears to be in labor. If the cervix seems to be rigid, or "non-negotiable," as Potter says, I would administer a hypo of dilaudid gr. $\frac{1}{32}$ and scopolamine gr. $\frac{1}{200}$ and probably stop the labor, rather than encourage it. On the other hand, if it appears that some progress has been made and the patient is not tired, I might consider rupturing the membranes. If progressive labor did not ensue, I would proceed with small doses of pituitrin as outlined by Dr. Eastman, and if response were then slow, would also order an enema.

Secondary inertia implies that after a certain amount of progress had been made resulting from a normal type labor, retardation occurs due to ineffective uterine contractions. If the patient is not tired, rupture of the membranes will usually re-establish an effective labor. If the response should be slow, a hot enema and a small dose of pituitrin

by hypo will usually accomplish desirable results. If it is evident that the patient and uterus are tired, she should be given several hours of rest, followed by appropriate stimulation such as enema, small dose of pituitrin, or rupture of membranes, depending upon the degree of stimulation that seems appropriate.

I believe there is danger in the repeated use of pituitrin over a long period of time. One case of Dr. Eastman was given nine injections of small doses at 30-minute intervals. Perhaps that was not a factor in causing rupture of the uterus in that particular case. However, I do believe that if one tries to stimulate a tired uterus hour after hour, the condition becomes aggravated. Frequently, the patient and her uterus need a good rest, followed by the procedure previously described. It is inadvisable to whip or push a tired uterus. The importance of rest should not be overlooked.

DR. HAROLD L. GAINEY, Kansas City, Mo.—I disagree with those who think that this paper might have a deleterious effect on the general man. My reason for not giving pituitrin in these prolonged labors is not the disproportion between the fetus and cervix, but due to a cervix which is not ready to dilate, and perhaps these poor contractions are a physiologic response to a cervix not prepared for labor. I would be very much interested in knowing if Dr. Eastman has noted that particular difference in the cervix of a patient in prolonged labor, and rather than to concentrate on inertia and disproportion, is it not a safe physiologic response to a cervix that is not physiologically at term and ready for dilatation? I have seen a case where the contractions became so severe that we had to relieve the intensity of the contractions both for the safety of the mother and the baby.

DR. M. PIERCE RUCKER, Richmond, Va.—How do you differentiate the constriction ring always from the simple inertia?

DR. EASTMAN (Closing).—Dr. Williams has made some very astute and practical comments. Artificial rupture of the membranes is a most valuable procedure. I do not have the exact figures with me, but somewhere between 85 and 90 per cent of the patients in the series reported had ruptured their membranes spontaneously prior to the use of pituitrin. Of course, the management of uterine inertia is made much safer today by the use of penicillin and sulfonamides.

I would answer Dr. Williams' question in the negative, that is: uterine inertia does not tend to repeat.

The question was brought up by Dr. Jacobs and several others as to whether we were doing the right thing in condoning in any way the use of pituitary extract, because it would be a bad teaching principle to go out from this Association. Dr. Quigley says that in Rochester the doctors are not using pituitary extract. That does not hold true in Maryland, and I have a feeling that general practitioners throughout the country, despite all the emphasis on the dangers of it, are employing it and in large doses, and I do not think we should be so naïve as to think that any statement from this Association is going to have much effect on those men. They have tried it and achieved good results most of the time, and will continue with its use. It is my feeling that emphasis on contraindications and small dosage might do more good than the recommendation to eliminate its employment entirely.

I am very much perplexed as to how to answer Dr. Rucker's question about constriction rings. I know of his experience and I read with great interest Dr. Herman Johnson's paper stating that he had one constriction ring in every 80 labors. We must miss a great many of these constriction rings because we do not see them with such frequency as that, but it may be that many of our uterine inertia cases might be called by others constriction rings. We see what we say is a constriction ring once or twice a year, and even then are inclined to put a question mark after the diagnosis.

Dr. Gainey asked about the cervix. Many of these patients with prolonged labors have unfavorable cervices, but what can be done about it? The condition is part of the picture.

AN ANALYSIS OF DEATHS FROM POSTPARTUM HEMORRHAGE*

CLAYTON T. BEECHAM, M.D., PHILADELPHIA, PA.

(From the Maternal Welfare Committee of the Philadelphia County Medical Society)

DURING the fifteen years 1931 to 1945 inclusive, there were 520,489 deliveries in Philadelphia. Over this fifteen-year period there were 1,987 maternal deaths, for an average of 38.17 in every 10,000 deliveries, i.e., live and stillbirths. We wish to point out that in this study all figures (both for the United States and Philadelphia) are based on total births. It is customary to express mortality figures in the "number of deaths per 10,000 live births." Following that line of analysis we would exclude from this study many women who perished along with their babies in obstetrically preventable deaths. For this reason we believe that an analysis of postpartum hemorrhage deaths per live births does not give a true picture of obstetric events (Fig. 1).

This also shows the annual deliveries, the maternal mortality, and mortality from postpartum hemorrhage over the fifteen years under discussion. The top line illustrates the influence of economic conditions and war on birth rate. The second line in the graph illustrates the maternal mortality in Philadelphia. Here we start with the disgraceful figure of 248 deaths, or 70.28 in every 10,000 deliveries, for the year 1931. More significant, this date marks the beginning of the activities of the Maternal Welfare Committee of the Philadelphia County Medical Society under the able leadership of Philip F. Williams. The consistent downward trend of this second line in spite of an increased birth rate during the past six years proves the value of this committee's work. In 1945 there were 81 deaths in 39,956 births, or 20.27 per 10,000, for a reduction in maternal mortality of 50.01 per 10,000 deliveries in fifteen years.

In Fig. 2 we have shown the mortality rate for the United States during the years 1931 to 1943 inclusive, along with the rate for Philadelphia. Except for three years, the Philadelphia figures were an improvement over those for the nation. Notwithstanding, there remains one set of mortality figures at a constant level over the years—those for postpartum hemorrhage. To amplify the small but constant group of cases shown in Fig. 1, we have enlarged the picture in Fig. 3. This represents 168 deaths from postpartum hemorrhage or 8.45 per cent of the total in fifteen years. The average is 11.2 deaths from this cause a year. The sharp rise in the year 1932 was due to Philadelphia's one excursion into the realm of manual dilatation of the cervix and version.

Though the deaths from postpartum hemorrhage remain small and constant in number, the Maternal Welfare Committee has judged 121, or 72 per cent, of these deaths to be preventable (Table I). One hundred five or 62.5 per cent were judged preventable deaths due either to errors in judgment or technique on the part of the attending obstetrician. The patient either through carelessness or ignorance was held responsible for her own death in 9.5 per cent of the cases.

General Considerations

Home deliveries have gradually declined throughout the country over this fifteen-year period, and this is also true for Philadelphia. Of the deaths from postpartum hemorrhage, 21 patients were delivered and died at home, while four were delivered at home and died in a hospital.

*Read at the Fifty-Seventh Annual Meeting of the American Association of Obstetricians, Gynecologists, and Abdominal Surgeons, Hot Springs, Va., Sept. 5 to 7, 1946.

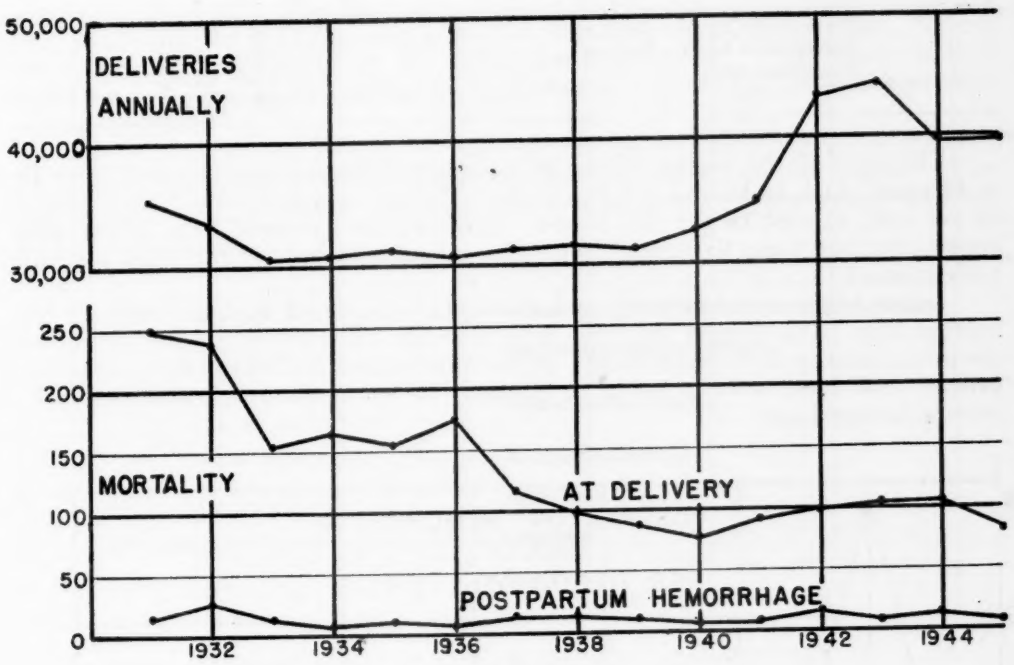
50,000
DELIVERIES
ANNUALLY
40,000
30,000
250
200
150
MORTALITY
AT DELIVERY
100
50
POSTPARTUM HEMORRHAGE
0
1932
1934
1936
1938
1940
1942
1944

Fig. 1.

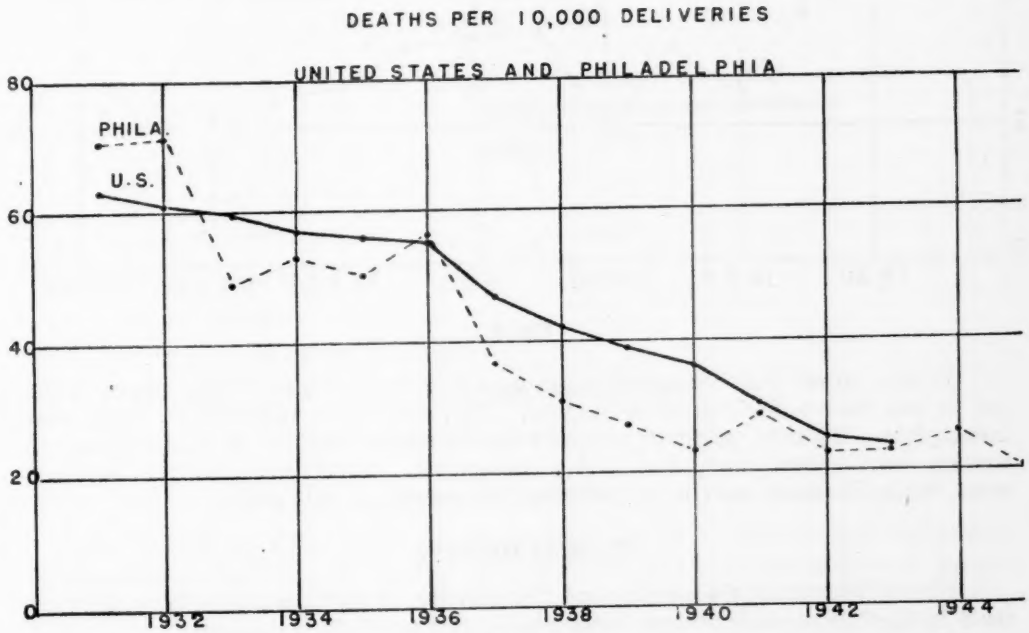
DEATHS PER 10,000 DELIVERIES
UNITED STATES AND PHILADELPHIA
80
PHILA.
U.S.
60
40
20
0
1932
1934
1936
1938
1940
1942
1944

Fig. 2.

TABLE I. DEATHS FROM POSTPARTUM HEMORRHAGE

Preventable by the Doctor	105— 62.5%
Preventable by the Patient	16— 9.5%
Nonpreventable	47— 28.0%
Total	168—100.0%

The ages of the women dying of postpartum hemorrhage ranged from 15 to 44 years, with an average of 31.5 years. The group was predominantly white, 84 per cent, against 16 per cent Negro. These women averaged four pregnancies apiece, and had three living children. The largest number of pregnancies in any patient was 17.

Labor began spontaneously and membranes ruptured spontaneously in the average case. The longest recorded labor was one hundred fifty-eight hours, but the group averaged fourteen hours. In the vast majority of cases one was not impressed with long labor as being an etiologic factor in the development of postpartum hemorrhage.

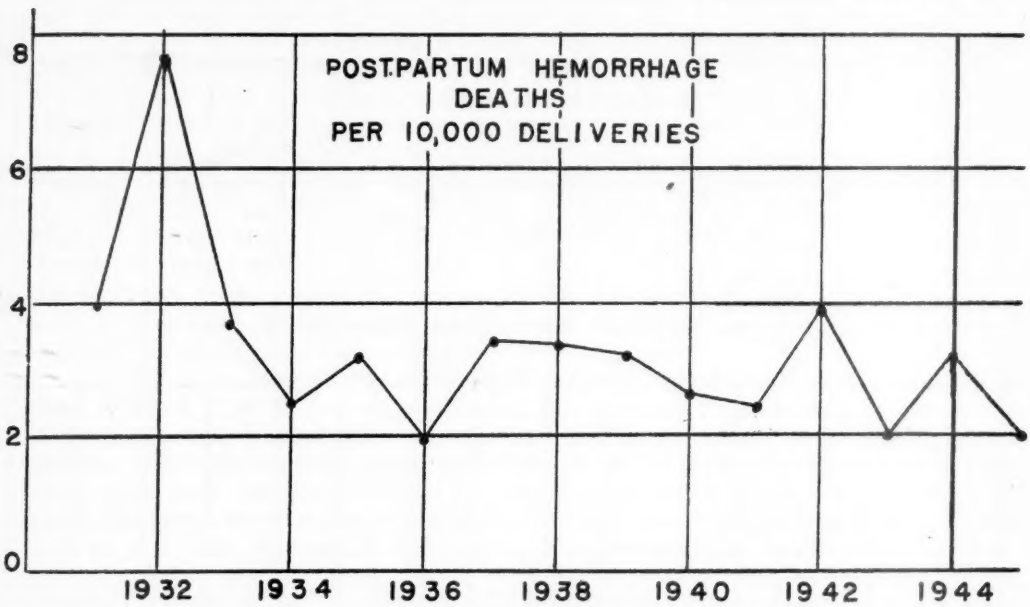

Fig. 3.

It was hoped that information on analgesic agents used might prove fruitful in our search for causative factors. The records in this regard were most incomplete. Twenty patients received barbiturates, usually in small doses, 15 women were given morphine and scopolamine. Sixty-three women received none, while 70 charts carried no information regarding this point.

Type of Delivery

Fig. 4 illustrates the percentage distribution of various methods of delivery used in the 168 women. There were five sets of twins in the group.

One-third of the patients delivered spontaneously, while the remaining two-thirds had various obstetric operations. The committee felt that some of the operations were indicated, but the vast majority were not. Manual dilatation of the cervix and version was uniformly condemned. This operation reached

its highest popularity in 1932. Since then its frequency in fatal cases has gradually declined. The Maternal Welfare Committee justly takes credit for this awakening by holding open and free discussion on all these cases. No one could fail to be impressed by the difficulties encountered by extremely skillful operators. It was in this group of cases where a very high incidence of stillbirths occurred.

As a factor in the etiology of postpartum hemorrhage, operative obstetric procedures must receive first line attention. Complications ran higher where interference was practiced, although the spontaneous delivery group was not free of complications.

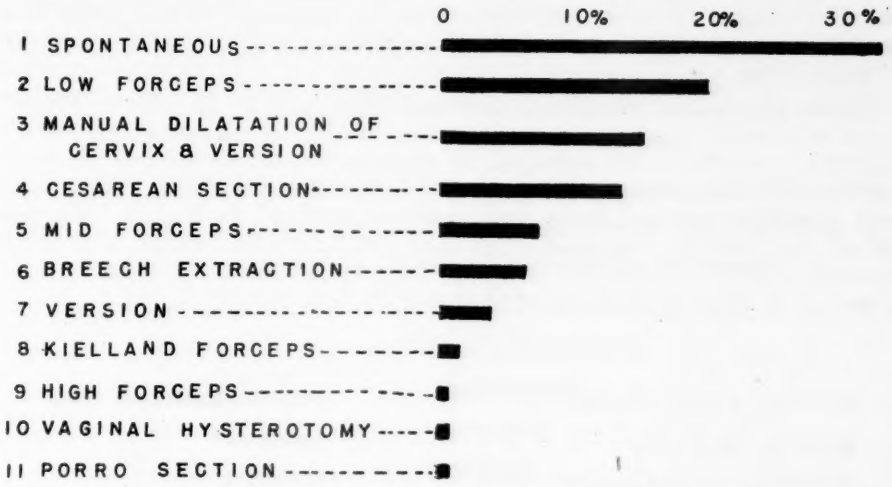

Fig. 4.—Type of delivery; percentage distribution.

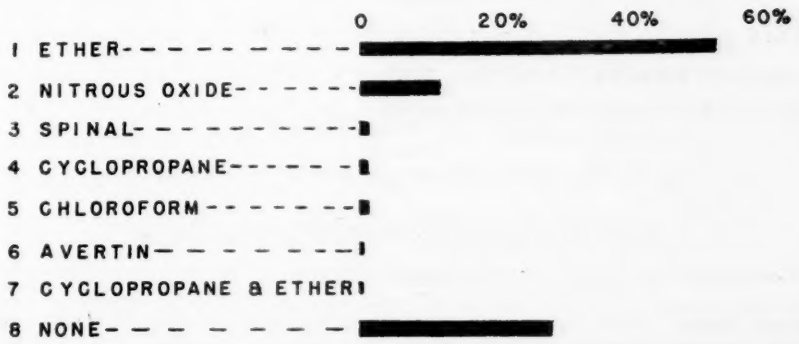

Fig. 5.—Anesthesia; percentage distribution.

Type of Anesthesia

In Fig. 5 we show the percentage distribution of the various anesthetic agents used in the 168 cases. It is interesting to note that 29 per cent of the patients had no anesthesia and as previously pointed out 33 per cent delivered spontaneously. This is scant difference. Therefore from our figures, one could state that a patient delivering spontaneously without anesthesia is just as liable to hemorrhage as the patient with an operative delivery and general anesthesia. Unfortunately, we have no data on regional anesthesia, there being only two cases where spinal was used. The fact that local, caudal, and essentially spinal

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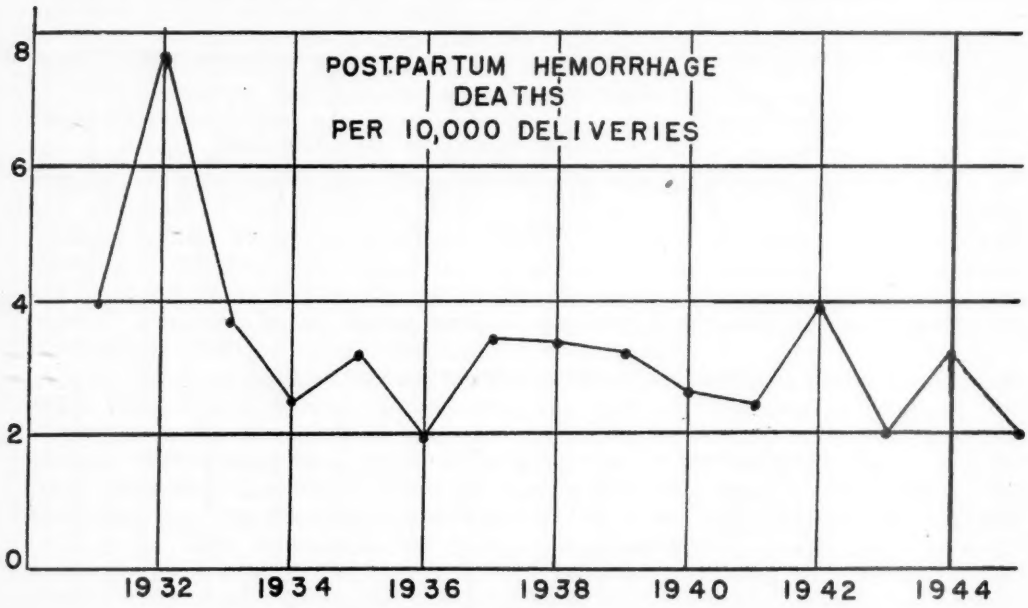

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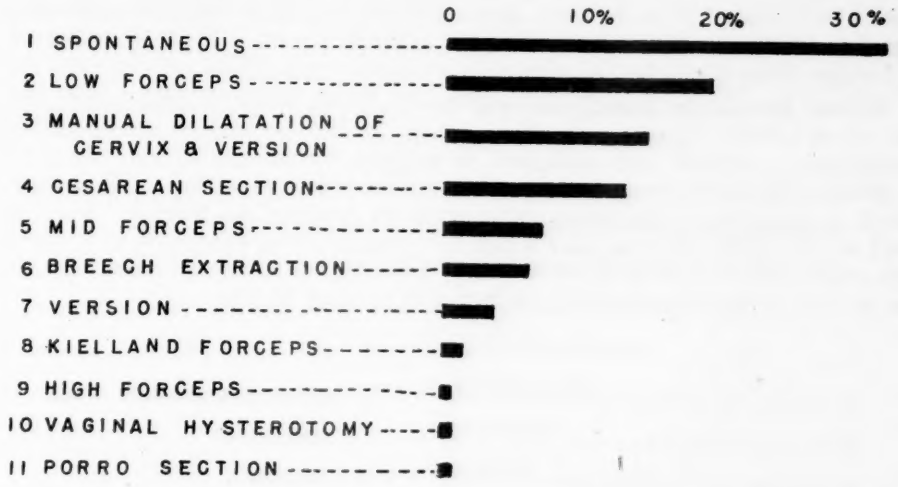

Fig. 4.—Type of delivery; percentage distribution.

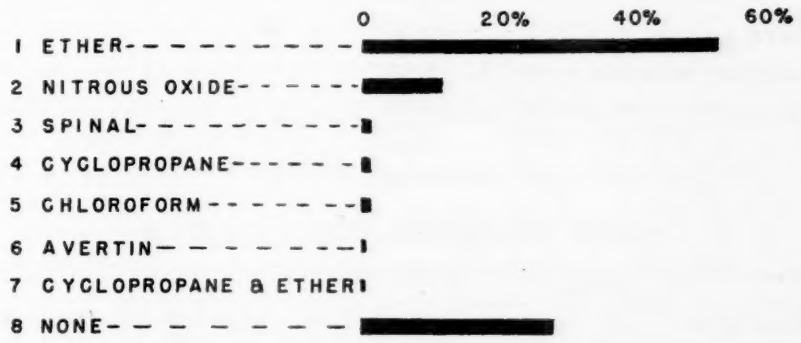

Fig. 5.—Anesthesia; percentage distribution.

Type of Anesthesia

In Fig. 5 we show the percentage distribution of the various anesthetic agents used in the 168 cases. It is interesting to note that 29 per cent of the patients had no anesthesia and as previously pointed out 33 per cent delivered spontaneously. This is scant difference. Therefore from our figures, one could state that a patient delivering spontaneously without anesthesia is just as liable to hemorrhage as the patient with an operative delivery and general anesthesia. Unfortunately, we have no data on regional anesthesia, there being only two cases where spinal was used. The fact that local, caudal, and essentially spinal

anesthesia are missing from the list brings up an interesting point. We know these agents have been increasingly used in Philadelphia. One could maintain that the very absence of regional anesthesia from the list proves that it is the method of choice as a safeguard against postpartum hemorrhage.

Here we are faced with the old saying that anything can be proved by figures. I feel that these data are inconclusive and must be re-evaluated after another time interval, when regional anesthesia is as widely used as general anesthesia.

The Third Stage of Labor

One-third of the patients were given a pituitary solution at the beginning of the third stage of labor, and some ergot preparation at the completion of placental delivery. The remainder had oxytocics used only at the end of the third stage (Fig. 6).

Where inhalation anesthesia was used for delivery it was continued, in spite of abnormal bleeding in many cases, until the placenta was delivered. Suprafundal pressure was sufficient to express two-thirds of the placentas in the group, and 12½ per cent were removed at cesarean section. The remainder offered complications and were dealt with as outlined in Fig. 6. Manual removal of the placenta was done when the bleeding was excessive, and the third stage could not be completed otherwise. Late manual removal was done after a long period of bleeding and the patient was in deep shock.

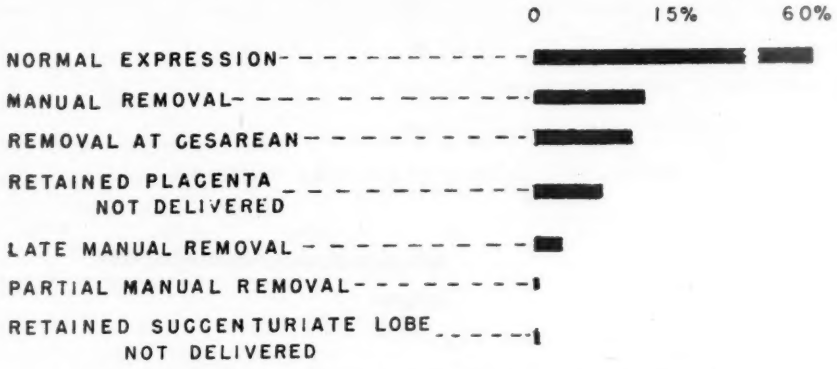

Fig. 6.—Placental management; percentage management.

TABLE II. ETIOLOGY OF POSTPARTUM HEMORRHAGE

ETIOLOGY	NUMBER	PER CENT
Atonic uterus	75	44.64
Atonic uterus following placenta previa	25	18.89
Atonic uterus following abruptio placenta	15	8.92
Atonic uterus following twins	5	2.97
Atonic uterus following hydramnios	1	0.59
Retained placenta—not delivered	12	7.15
Inversion of the uterus	11	6.54
Ruptured uterus	7	4.16
Lacerated cervix	7	4.16
Myoma uteri	4	2.38
Lacerated cervix and lower uterine segment	1	0.59
Lacerated upper vagina	1	0.59
Bleeding uterine incision	1	0.59
Bicornate uterus	1	0.59
Retained succenturiate lobe	1	0.59
Retained cotyledons	1	0.59

Etiology of Postpartum Hemorrhage

In Table II we have listed the apparent causes of fatal hemorrhage. Seventy-two per cent of the cases fell into the atonic uterus group. Why the uterus was atonic could not be determined, except in those patients having placenta previa, an abruption, twins, or hydramnios.

There were 11 cases of inversion of the uterus. The inversion was usually complete, although there were two partial inversions diagnosed at autopsy. None of these had the uterus replaced. One institution leads the others in this complication.

Overdistention of the uterus from either multiple pregnancies or hydramnios is generally conceded to be a very important cause of postpartum hemorrhage. This was not borne out in our study. Possibly the expectation of hemorrhage in such cases led to careful planning and complete treatment, with a lowered resultant death rate in these patients. Data on that score is not available, however.

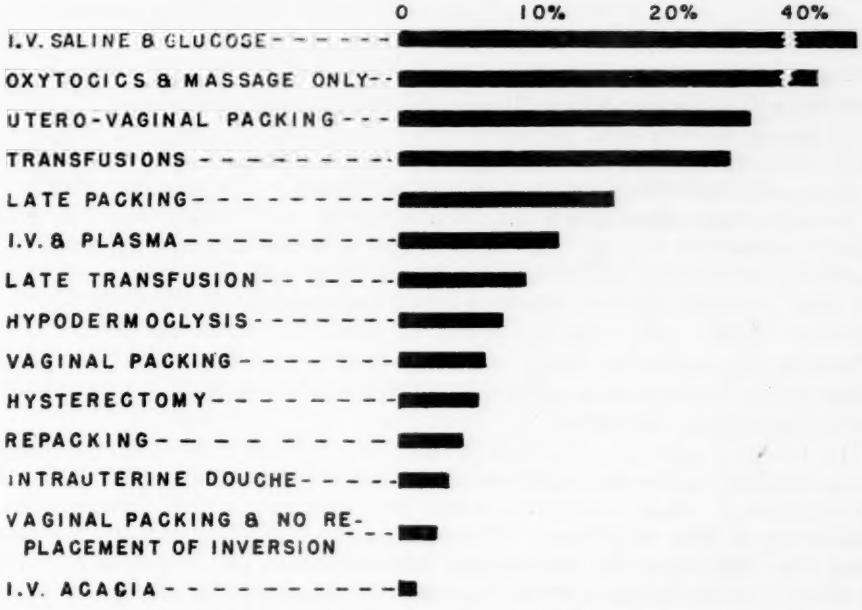

Fig. 7.—Treatment; percentage distribution.

Treatment

Fig. 7 lists the active treatment given these fatal cases. It is worth while to consider the therapeutic measures employed in detail, remembering that many patients received several of the listed instruments.

Forty-one and one-half per cent of the patients were allowed to bleed to death with nothing more than uterine massage and oxytocics being used. Forty-four and one-half per cent received intravenous fluids, while 25 per cent received blood transfusions. Essentially the same patients received blood as were packed in the orthodox fashion.

Late packing when the patient was practically moribund was used in 16 per cent, while by the same criteria late transfusions found employment in 9½ per cent. It might be interjected here that only two patients were given more than 500 c.c. of blood before death. Plasma, although a partial substitute for whole blood, certainly seems indicated until blood is available; yet it was only

used in 12 per cent. In 6½ per cent of the cases the attending physician could not explain to the Committee's satisfaction why the patient had vaginal packing only.

Hysterectomy was used in 6 per cent of the cases. In general, this group received energetic, organized, and recognized therapy. They were patients getting blood, adequately packed, bleeding through their packs and shock deepening. It would appear that the operation increased shock and hastened the fatal outcome, probably because the amount of blood given was insufficient.

Clinical Picture

The average time between delivery and death from postpartum hemorrhage was five and one-half hours. There was usually ample time for adequate treatment. All too often continuous "seepage" or "oozing" of blood from the introitus went unnoticed by attendants, the proper diagnosis only being made when the patient slipped into shock.

Discussion

Prophylaxis.—Study of these 168 case reports of postpartum hemorrhage reveals many factors overlooked and too often gross carelessness. One of the glaring omissions was good prenatal care. We think of ourselves as administering the prenatal period with utmost care in Philadelphia. Private doctor and free clinic alike saw the patients a regulation number of times and classified their care as adequate. How much time was spent in diet instruction as a means of physically conditioning the patient for her ultimate labor? There was ample opportunity with these patients since 96 per cent had supposedly adequate prenatal care. A few case reports mentioned the general physical condition of the patient as "poor," yet neglected to say in what manner it was poor.

In the prevention of many obstetric—not to mention fetal—complications, the best possible nutritional state is essential. Evidence of appreciation of this factor is lacking in this series.

An integral part of nutrition is the blood picture. Most of the charts carried no notation as to the blood count during the prenatal period. In other instances where a blood count was done, and medication for anemia prescribed, no follow-up studies were done. The patient entered labor without the physician having any idea what the hemoglobin and red blood cell count were. We have seen all of the well-known preparations for combating the anemia of pregnancy fail utterly in correcting this condition. In such instances, there is only one way to prepare such a patient for labor, and that is transfusions in the last four weeks of gestation.

This entire series is impressive from the standpoint of almost total disregard for the necessity of combating anemia in pregnancy as an aid to the treatment of a possible postpartum hemorrhage.

A third factor in the prophylaxis of hemorrhage is routine typing of all prenatal patients. A card is given to all patients during their routine visits, as shown. It is standard procedure to take Wassermanns on all prenatal patients, and it rapidly is becoming routine to do an Rh determination. It is a negligible expense to have the blood typed at the same time. Thus the patient brings the card from the clinic or private doctor with her to hospital admissions when she enters in labor. The saving of time in calling for donors or on the ever ready "blood bank" in an emergency is evident.

Prophylaxis against hemorrhage is carried further in labor. Our Committee records are incomplete on sedation used or its judicious application. There was even less evidence of measures employed to combat fatigue and ex-

DEPARTMENT OF
Obstetrics and Gynecology
Temple University Hospital

Name_____

Date_____

Blood type_____

Rh factor_____

Important: Keep this card in your purse. In a present or future pregnancy, or in the case of receiving a transfusion, its information is important.

haustion. From the Committee findings it is safe to assume that little attention was directed at these important factors.

In our search for factors contributing toward postpartum hemorrhage let us next consider anesthesia. It is generally conceded that deep inhalation anesthesia relaxes the uterus, yet I am sure all cases were not carried into a deep plane. It must be remembered that 49 patients delivered without anesthesia. Lacking more complete figures on regional anesthesia one cannot draw a conclusion. Individual case analysis, however, usually demonstrates that there were many errors in any given case with anesthesia adding to the grand total of mismanagement.

Management of the third stage of labor has been the subject of many noteworthy papers. Its importance in general prophylaxis against hemorrhage is well known. We cannot go into all the different techniques advocated by many careful observers for the management of the third stage. Here are some of the obvious errors picked up by the Committee's work:

1. The patients would deliver and the attendant would leave the third stage to some intern or nurse, inexperienced in the signs and symptoms of hemorrhage.
2. Inhalation anesthesia was continued, uninterrupted, through the third stage, although the patient was bleeding excessively.
3. Constant palpation of the uterus or holding of the fundus was not practiced in many instances.
4. In 12 cases the placenta was allowed to remain in the uterus while the patient bled to death, and nothing more than suprafundal pressure was used.
5. In 11 cases inversion of the uterus with no replacement or adequate fortifying treatment occurred.
6. Immediately after delivery of the placenta, the minimum one-hour period of close observation in the delivery room was not carried out.
7. Many patients bleeding abnormally after the placenta was delivered did not receive immediate packing and further measures of control. They were treated energetically only when shock was imminent.

In discussing the etiology of any of these fatal cases of postpartum bleeding, it would seem presumptuous to ascribe a single cause of hemorrhage. There were 75 instances of bleeding from an atonic uterus. What made the uterus atonic would in most cases add up to multiple factors ranging from inadequate prenatal care to choice of anesthetic. The atonic uteri encountered in placenta previa are to be expected from the flaccid lower segment. Once the correct diagnosis was made in placenta previa cases the physician usually forgot that he was dealing with an area in the uterus that is well known for its lack of contractile power. Such being the usual behavior of the lower segment, it would seem expedient to pack all cases, whether they are delivered vaginally or by cesarean section.

Montgomery advocates a technique that we have followed for some time and have found to be a most reliable method of forestalling postpartum hemorrhage in previa cases. The vagina is packed tightly at the time the patient is examined prior to section; at cesarean section the uterus is tightly packed. Thus the lower segment is held securely between two packs. With adequate amounts of blood the Montgomery method has given the best results we have yet seen. The Committee has not had a mortality report where this method was used. The deaths from abruptio placenta as those from placenta previa were negligible when the patient had been packed and received adequate blood.

Treatment in the majority of cases was far from ideal. First, there was the failure to utilize oxygen. Second, uterovaginal packing was used in only 26½ per cent of cases. Third, transfusions were given to only 25 per cent of the patients at a time when it could help. The amounts of blood used were inadequate, since the average was only 500 c.c. The Committee feels that these measures more than anything else are important in combating hemorrhage. It is understood that oxytocics, Trendelenburg position, stimulation, etc., are in order, but cannot compare with the three major forms of treatment.

Transfusions of whole blood are essential to the saving of life. We have seen the failure of small amounts as employed in this series, and, for the most part, they constituted token resistance only to the threat of death. It must be remembered that blood must be replaced in amounts lost. We have seen cases where as much as 3,000 c.c. were required before a patient could maintain her pulse and blood pressure without continuous oxygen, and at that time be considered out of danger from further hemorrhage.

Conclusions

Postpartum hemorrhage death was caused by several factors in most cases. They may be summarized as:

1. Carelessness.
2. Inadequate prenatal care.
3. Inadequate care during labor or operation.
4. Ill-advised operations and meddlesome obstetrics.
5. Poor choice and use of anesthesia.
6. Poor management of the third stage of labor.
7. Failure to recognize hemorrhage in time.
8. Insufficient use of oxygen, packing, and whole blood to combat hemorrhage.

We are indebted to Dr. J. Marsh Alesbury for permission to use the committee records, to Miss Dorothy Malhiel for supplying the vital statistics of Philadelphia, and E. E. Schwartz, Children's Bureau, for supplying the National figures.

GERMANTOWN PROFESSIONAL BUILDING

GREENE AND COULTER STREETS

Discussion

DR. G. D. ROYSTON, St. Louis, Mo.—I am surprised that so few of Dr. Beecham's cases were attributed to the anesthesia given.

My remarks will be directed to those cases of postpartum bleeding that predispose to complications following delivery. It is in this particular group that I feel inhalation narcosis is the most common cause. Among more than 35,000 deliveries on our obstetric service at the Washington University School, the great majority of them purely normal cases, chloroform was administered for the immediate delivery and repair. Naturally, it is not used in toxemic, dehydrated, or other abnormal conditions.

All inhalation narcoses and many local means for analgesia require expert administration for satisfactory results. The fear instilled and the lack of training in the proper administration of chloroform are to be deplored.

Most anesthetists, whether physicians or from a school of anesthesia, know little or nothing of its use in obstetrics. Two or three cubic centimeters dropped slowly on the open mask should suffice for the average delivery and repair. Among 4,000 consecutive deliveries under ether, carefully studied and analyzed, 16.6 per cent of the infants were more or less apneic at birth. Where ether is given for delivery, either the patient failed to get satisfactory analgesia, or she was given too much ether and lost too much blood. Among all the anesthetic or analgesic agents employed, ether administration was followed by the highest incidence of postpartum bleeding, *if* analgesia was attained.

DR. ROLAND S. CRON, Milwaukee, Wis.—I wish to mention an additional possible cause of late postpartum hemorrhage. In the past, large doses of stilbestrol have been administered to relieve the engorgement of breasts during the weaning period. We have seen more and more patients experiencing profound and sometimes exsanguinating hemorrhage following the administration of 15 mg. to 20 mg. of the drug on the third to the sixth postpartum day. Bleeding occurred three to four days later. Curettage and packing were necessary to control the hemorrhage. The curettings showed no evidence of retained placental tissue and only degenerated muscle and blood vessels.

We suspect that the stilbestrol may have some effect upon the end arteries and we know that there is a lag of two to three days between the time of administration and the bleedings from the arterioles. Since stilbestrol therapeusis is questionable in its efficacy for the relief of breast engorgement, and since postpartum hemorrhage may be associated with its administration, we suggest the discontinuation of its frequent use during the postpartum period.

DR. FREDERICK H. FALLS, Chicago, Ill.—There is one prophylactic measure that we have developed in Chicago in our clinic which we feel is of some value. We supply our patients with a tag, similar to the dog tag used in the army, stating the Rh factor and also the blood type. The patient wears this until she has been delivered. In case a patient has a bad acute or postpartum hemorrhage and is taken into an institution where her laboratory record is not available, at least her Rh factor and blood grouping are known.

DR. IRVING W. POTTER, Buffalo, N. Y.—I would like to talk particularly about our own management of these cases. We pay particular attention to the anesthetic, and for years we have dwelt persistently on the use of chloroform. Now it is an unfortunate matter when you consider that the young man who gives the anesthetic in the average hospital has probably never had a bottle of chloroform in his hands. Just as Dr. Royston has told you, they are afraid of it; and I am very sorry to feel as I do toward the teachers of anesthesia, that they are neglecting to teach these individuals the intelligent use of chloroform. It has been my experience that if you want to get a good chloroform anesthetizer, you have to get the older man.

There are other things to be considered, and one is the management of the third stage of labor. It is surprising to watch men finish up the third stage. If you wait, the placenta will slide out of the vaginal canal with very little bleeding.

DR. BEECHAM (Closing).—There has been much discussion concerning anesthesia. I must admit a deep prejudice against general anesthesia in obstetrics and gynecology. A review of the 168 records failed in the main to establish general anesthesia as the single etiologic factor in postpartum hemorrhage where it was employed. Rather, multiple factors along with poor choice and administration of a general anesthetic seemed to be the causative agents.

Dr. Royston emphasized rapid packing of a bleeding uterus. We are certainly in accord with this procedure. Packing is best employed when the bleeding has been present several minutes with no sign of decreasing, and before there is an alteration in pulse rate.

We have found nothing in patients who were packed to support the claim that packing increases the incidence of puerperal sepsis. It is surprising to note that many students are taught that packing leads to sepsis. These same students as encountered in National Board Examinations will try to stop hemorrhage by the formidable procedure of putting clamps on the uterine arteries through the lateral vaginal fornices.

Dr. Montgomery has made two important contributions to the prophylaxis of hemorrhage, i.e., the two packs for placenta previa and the "blood type card."

There is another point in prophylaxis that has not been mentioned, i.e., the routine use of whole blood during cesarean section. It is a rule in our hospital along with many others that a patient must have intravenous fluids running, and blood in the operating room before the section is started. This precludes the sudden shock and collapsed veins one occasionally sees in cesarean sections. This has been a most valuable prophylactic step.

THE TREATMENT OF AMENORRHEA IN YOUNG WOMEN*

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(From the Section on Obstetrics and Gynecology, Mayo Clinic)

THE conditions associated with the occurrence of amenorrhea lasting from one to five years in 94 women between the ages of 19 and 25 years were discussed in a previous paper. These conditions were tumors in seven cases, anorexia nervosa in 15, failure of the pituitary body in 36, failure of the ovary in 17, and primary amenorrhea in nineteen. The seven patients in whom tumors were found are excluded from consideration in this paper, leaving 87 patients whose treatment is to be discussed herein. The importance of the history, physical examination, and various laboratory tests was emphasized in determining the reason for the amenorrhea and classifying the deficiency. This seems of great importance. One is often asked for advice in the treatment of a patient who has amenorrhea. I doubt that one may safely generalize without knowing as much as possible about the given patient, and then treatment becomes individualized for that patient. For example, treatment with roentgen rays to the pituitary body or with extrinsic gonadotropins for a woman who has excess amounts of prolan in the urine, or who clinically presents the picture of menopause praecox, is not rational.

The procedures to be mentioned herein represent those employed in the treatment of the aforementioned group of 87 young women.

Nutrition

Nutrition assumes great importance in all bodily functions of the young person. One frequently finds some disturbance of the function of menstruation in women who are considerably under- or overweight. The extreme example of variation in weight associated with menstrual disturbances is seen in the patient suffering from functional anorexia or anorexia nervosa. These patients should serve to emphasize the basic necessity of a balanced ration rich in proteins and vitamins. The tissues concerned with the menstrual function in the young seem particularly sensitive to deprivation of these elements. When the patient is markedly underweight or anorexia nervosa exists, it must be remembered that a daily caloric intake well above the daily caloric requirement for that particular patient must often be maintained for several months before the patient regains her normal weight. Young women suffering from anorexia nervosa have so restricted the quantity and quality of their intake of food that the patient and her gastrointestinal tract must be re-educated. Our procedure for the treatment of this condition has been outlined by Berkman[1] as follows:

An estimate of the patient's previous daily caloric intake is made. To this amount is added 300 calories. The patient is served a high-protein, high-vitamin

*Read before the Fifty-Seventh Annual Meeting of the American Association of Obstetricians, Gynecologists and Abdominal Surgeons, Hot Springs, Va., Sept. 5 to 7, 1946.

diet based on that number of calories (usually from 1,300 to 1,500 calories), and is asked to eat everything served her. For the first few days the patient may complain of distress and a sensation of fullness. However, after several days these symptoms gradually become less. After five to six days the caloric content of the diet is increased by another 300 calories. For a few days discomfort after eating may again appear. This procedure is repeated until the caloric intake is between 3,400 and 3,600 calories.

The behavior of the basal rate of metabolism usually is typical when these patients respond to the above regime. Many of them have rates well below –20 per cent, some as low as –35 per cent. Coincident with the gain in weight the rate of metabolism will return to normal without the administration of thyroid extract. Indeed, this medication is poorly tolerated and actually may impede recovery of these patients.

It must be kept in mind that most of these young women suffering from anorexia nervosa previously had been healthy and had experienced normal menstruation. Evidence of malfunction did not appear until the glands of internal secretion concerned with menstruation were deprived of a normal internal environment. Until there is return to a normal nutritional state, and thus a normal environment, we may not rightly expect functional activity of these glands. When such a state has been reached and menstruation has not recurred, we may then commence hormonal or other therapy aimed to further stimulate function. The cyclic administration of estrogens may, however, be commenced as soon as feasible in an attempt to shorten the period of uterine atrophy usually seen in these patients.

Cyclic Therapy With Estrogens

Where there has been considerable reduction in the size of the uterus, and particularly when microscopic examination of the endometrium reveals atrophy, it is advisable to commence the cyclic administration of estrogens, either for two or for three weeks in four. This can be accomplished with various preparations. One of the simplest methods is to use diethylstilbestrol to the daily limit of tolerance. Other preparations for oral and parenteral administration, of course, can be used. This form of treatment serves at least three purposes. First, it primes the uterus and endometrium and tends to prevent further atrophy. Second, stimulation of the pituitary body may be encouraged by simulation of the cyclic rise and fall of bodily estrogens that occur under normal conditions. A more complete imitation of this may be achieved by combining estrogens and progesterone in the therapeutic program. Third, if adequate amounts of these substances are used, and the uterus and endometrium make no response, we may assume that the Müllerian duct is naturally unresponsive and therefore may be a contributing factor to the amenorrhea.

The presence of estrogens is responsible for the distinguishing characteristics of women, and for the integrity of the physiology of the menstrual and reproductive cycle. Therefore, it seems desirable to attempt to restore levels in the body to within normal limits as soon as possible.

Thyroid Extract

The relationship of thyroxin to the physiology of the genital tract is not definitely known, except that the general efficiency of the body is enhanced when sufficient amounts of this substance are present in the body. Accordingly, the efficacy of thyroid extract in the treatment of amenorrhea in properly selected cases is widely recognized. However, there are certain important considerations that should be discussed.

One should be certain to determine the patient's actual basal level of metabolism before initiating treatment. Often more than one estimation of the rate is necessary. When this has been determined, one has a point from which controlled treatment can be commenced and followed through by repeated estimations during the course of treatment.

As a rule, we prefer to elevate the rate rather abruptly. For example, with a basal metabolic rate of between minus 15 and minus 20 per cent, the patient is given 3 to 4 grains (0.19 to 0.26 Gm.) of desiccated thyroid substance for three days, 2 grains (0.13 Gm.) for three days, and then 1 to 1½ grains (0.06 to 0.1 Gm.) daily. Another basal metabolic rate is taken after the first week of treatment, and another after the second, after which it is usually possible to determine the maintenance dose. Occasionally, a longer period is necessary.

The patient is then instructed to be certain that the same brand of thyroid substance is always used, and is told that estimations of the basal metabolic rate are advisable from time to time for proper control of treatment. If any untoward symptoms seem to occur, the patient is asked to report. It is emphasized to that patient that the daily maintenance dose is to be continued indefinitely. Several months may elapse before the full effect of the readjustment of the basal metabolic rate will be effective.

The normal range of basal metabolic rates is stated to be between +10 and −10 per cent, and if a given patient's rate is within this range, treatment with thyroid extract frequently is not considered to be necessary. Often this is true. However, properly controlled treatment with thyroid extract offers a very effective and safe method of stimulating bodily function. Consequently, even if the basal rate is within the limits of −10 and zero in the presence of amenorrhea, elevation of the rate to +5 per cent may be considered, if it is properly controlled. If symptoms of intolerance occur and persist, the treatment can be stopped. I have seen instances in which elevation of a rate from −15 to −5 per cent was ineffective, but in which satisfactory results occurred where the rate was elevated further to +5 per cent.

In the presence of a lowered rate of metabolism or one that has been inadequately elevated, other forms of substitutional or stimulating therapy frequently are ineffective. Accordingly, we usually postpone other forms of treatment until the basal metabolic rate has been stabilized within normal limits. Frequently, when this occurs, no other treatment is necessary.

Roentgen Therapy

Low dosage roentgen-ray irradiation to the pituitary body or ovaries, or to both, has been employed safely and effectively at the Mayo Clinic since the

investigations of Drips[2] and Ford eighteen years ago. We have found that these treatments often would re-establish the menses, but the effect frequently wore off in a few months and needed to be repeated. It is also apparent that better results are obtained when amenorrhea of more than a year's duration is due primarily to pituitary rather than to ovarian failure. Dr. Drips, for example, has among her records those of twelve young women* whose amenorrhea of one year's to ten years' duration was attributed to failure of the pituitary body and who received only roentgen therapy to the pituitary body and ovaries. Seven of these patients experienced menstruation for a year at least, and two for a shorter period, an improvement rate of 75 per cent. Twenty-three young women who had amenorrhea of one year to seven years in duration due to ovarian failure were likewise treated with roentgen rays to the ovaries. Five of them improved for a year at least, and four were benefited for a shorter period, an improvement rate of 39 per cent.

When a lowered rate of metabolism is found in these patients, the rate is purposely elevated before the roentgen treatment, and, when the menses reappear, estrogens are administered cyclically. This combined therapy has been more successful than any single method.

In a group of 55 single women* of an average age of 22.5 years treated between 1930 and 1940, 21 were still single in 1945, and 14 (66.6 per cent) of the 21 were still having regular menses. Thirty-four had married and 26 (76.4 per cent) of these 34 reported their periods were still normal in 1945. These 34 women had already borne 38 normal children and had experienced two miscarriages. A few of the women had reverted to their previous status of amenorrhea after parturition.

Extrinsic Gonadotropins

Extrinsic gonadotropins have been but rarely employed by our group. Only three of the 87 patients concerned herein received them. We have preferred to make every effort to stimulate the patient's own pituitary body. If this can be done, certainly a more effective gonadotropin is produced. No doubt gonadotropic preparations have a place in the treatment of amenorrhea, as evidenced by the reported work of others.

Results of Treatment

Eighty-seven patients who had experienced amenorrhea for a year or longer were treated by combinations of the methods previously discussed in this paper. The follow-up period for this group of 87 patients has ranged from one year to six years, with an average of two years and three months.

Seventeen of the 87 patients experienced amenorrhea because of failure of the ovary to function; in 10 (58.8 per cent) of these 17 the menses reappeared after treatment.

Thirty-six of the 87 patients experienced amenorrhea associated with failure of the pituitary body; 26 (72.2 per cent) of the 36 responded to treatment.

*Not included in the present series of eighty-seven.

Fifteen of the 87 patients experienced amenorrhea in association with anorexia nervosa; eight (53.3 per cent) of the 15 responded to treatment.

Nineteen of the 87 patients had primary amenorrhea; three of the 19 (one aged 19, one aged 21, and one aged 23 years) began to have menses after treatment.

One should not accept these figures too literally. In another group of 87 patients better or poorer results might be obtained. One must apply himself to evaluation of the status and treatment of the individual patient.

Conclusions

We will agree that in these young women with established amenorrhea, every reasonable effort should be made to salvage the menstrual and reproductive functions. This salvage will never occur in 100 per cent of these cases of amenorrhea of long standing. Consequently, if an intensive trial of treatment is not successful, it may well be stopped. If the patient's own glandular functions will not carry on after therapy has been thus halted, little will be gained by further treatment.

It is well known that in general the shorter the duration of the amenorrhea, the better will be the response of the patient to treatment. The condition of those patients who present amenorrhea of less than a year's duration, therefore, offers a better prognosis as a rule than that of the group reported herein.

The aim of the plan of treatment outlined in this paper is, first, to secure an environment or general bodily condition in which the nonfunctioning or poorly functioning glandular tissues will have the best chance for function. Second, when this has been secured, effort is made to stimulate function and to maintain it.

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2. Drips, Della G.: Personal communication to the author.

Discussion

DR. GERALD W. GUSTAFSON, Indianapolis, Ind.—Individualization of the patient with correction of dietary deficiencies, general ill health, and anemias before institution of endocrine therapy seems rational. The recognition and correction of hypometabolism, hypo- and hyperthyroid states before other endocrine therapy is begun also seem advisable. When indicated, thyroid gives more brilliant results than any other endocrine substance, and often is sufficient therapy.

If the general health and metabolism of the individual are normal, it is then ideal to attempt to catalogue the patient as to whether there is ovarian or pituitary failure or a possible adrenogenital syndrome.

In cases of ovarian failure with atrophic endometrium, reduction in size of the uterus and with high urine gonadotropins, cyclic treatment is warranted. Recognizing that estrogens are merely substitutional, they are, as Dr. Randall has stated, necessary to prime the endometrium. It is probably ideal to follow with progesterone and Zondek, Rakoff, and others have reported encouraging results with large doses of progesterone. When the latter is given in large amounts, such as 20 mg. daily for three days, estrogens can be given for a shorter time with less tendency to inhibit the anterior pituitary. Rakoff recently reports improvement in the hormonal pattern, even in cases of gonadotrophic deficiency.

Though most of us have been reluctant to use irradiation, our experience at Indiana has, like Dr. Randall's, been encouraging. Dr. J. A. Campbell, our radiologist, has treated 24 cases of amenorrhea and sterility. All had had endocrine therapy and had not responded. These were given low dosage irradiation to the pituitary and ovaries. Normal menstruation followed in 17 cases. Three of these have delivered normal babies and a fourth is now pregnant. Treatment failed in 7 cases.

It is significant, I think, that the highest percentage of successes in Dr. Randall's cases were in those of pituitary failure, particularly as extrinsic gonadotropins were rarely used.

Finally, from the standpoint of the practical clinician, Dr. Randall has given us light and encouragement instead of the fog and contradiction often present in endocrinologic manuscripts. While the present-day treatment of amenorrhea is far from satisfactory, we need not be too pessimistic in undertaking it.

DR. WILLIAM R. BARNEY, Cleveland, Ohio.—I would like to ask about pregnancy following this treatment in Dr. Randall's cases?

DR. RANDALL, Rochester, Minn. (Closing).—In reply to Dr. Barney's question in regard to pregnancy following the treatment of amenorrhea, may I point out that the patients here discussed are all young, and very few of them are married. Consequently, the number of patients in whom pregnancy was a possibility is too small to warrant any conclusions.

SEROLOGY AND OBSTETRICS*

R. T. LaVake, M.D., Minneapolis, Minn.

EXPERIENCE acquired in quest of the cause of the toxemias of pregnancy would seem to suggest that we revise our interpretation of the significance of agglutinogens and isoagglutinins in the blood setups.

Due to the tremendous importance of blood transfusion as a therapeutic agent, attention has been focussed upon the agglutinogens and isoagglutinins from the gross transfusion standpoint, and with too little regard for their possible association with disease manifestations, which latter would seem to be due to nature's method of breeding cell substances in or out of the human species, in the inscrutable interests of evolution.

It is well understood that the possible death of the recipient of incompatible blood is due to the agglutination of the donor's cells by the action of the agglutinins of the blood of the recipient. It is not generally sensed that such incompatible blood may be actually poisonous to the cells of the recipient, and that, if the obscuring effects of agglutination and hemolysis could be obviated, we would note pathology in the recipient similar, in kind, to that found in the toxemia of pregnancy. This can be glimpsed, occasionally, in cases of delayed transfusion deaths, and even in disease manifestations following the intramuscular injection of, here defined, toxic bloods.

In nature, the nearest approach to transfusion occurs at times and in infinitesimal quantities between fetus and mother, and it seems evident that the blood setups are the evolutionary results of this contingency and possible filtration of antigens. The result presented would seem to point to the validity of the argument that the inherited agglutinins represent inherited antitoxic substances which constitute a modicum of protection for the female, who may, under the bisexual mechanism of propagation and under the laws of heredity, bear a fetus containing blood substances ancestrally and presently toxic to the type of cells that she possesses. These agglutinins are, as in bacteriology, merely one of the functional arms of antitoxic substances, the other arms being the lytic and opsonic. When you titer an isoagglutinin, you are titering the strength of the antitoxic substance from which it stems, and, as will be suggestively demonstrated later, if the antitoxic substance involved is not of sufficient strength to protect the mother, and if her cells are vigorous, they will secrete more of the same antitoxic substance, and the titer of the isoagglutinin may rise. The statement may rise, is used advisedly, and should be emphasized, because the true strength of the antitoxin may be masked by the antitoxin absorptive power of the fetal cells and antigens in solution; and again it can reasonably be assumed that it would not rise if the maternal cells were deficient in reactive vigor, or were overwhelmed. Under a combination of such con-

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tingencies it could reasonably be assumed that the agglutinin might fall in titer, or even disappear temporarily. Facts support these arguments.

There are so many variants involved that only in a comparatively few cases does the true mechanism reveal itself. These variants, if not envisaged, may mislead one in drawing conclusions from statistical data, however extensive the data may be.

From the disease standpoint, we are not dealing basically with agglutinogens and agglutinins, but with toxic substances and antitoxic substances. This concept of fetal toxins and maternal antitoxins furnishes a reasonable explanation of why it is that the group O mother inherits the anti-A and anti-B agglutinins: the group A mother, the anti-B agglutinin; and the group B mother, the anti-A agglutinin.

The antitoxic substance inheritance provides a modicum of protection for the mother, and operates against her interests, spelling her likely doom only in the event of gross transfusion of incompatible blood, a contingency that was not envisaged by nature.

If this be true, the question as to why the human possesses hereditary antitoxins against some substances and not against others would seem to be reasonably answered conjecturally by an ontogenic approach. At least the A and B substances, against which antitoxins are inheritable, can be demonstrated, according to Kemp, about the thirty-seventh day of gestation, and yet, the fetus' own complement of antitoxins does not appear until around the two hundred and eightieth day. It may be argued with reason, it would seem, that one can infer from this that it takes in the neighborhood of eight times longer for a specific antitoxic substance to become inheritable than for a cell substance to become inheritable. It may be that the substances against which no inherited antitoxins obtain may have entered the species too recently to permit of their specific antitoxins being yet inheritable. This would include the Rh group.

Adequate proof of a toxin-antitoxin relationship between child and mother with the involvement of disease demands that one isolate in the child a substance not possessed by the mother; that one demonstrate that she reacts to this specific substance either by the active production of an identifiable specific antitoxin where no antitoxin previously obtained, or by a functional change in titer of a pre-existing antitoxin; that during this process signs of disease manifest themselves in the mother, signs that follow a characteristic pattern, and that seem to bear a direct functional relationship with the toxin; that the severity of the manifestations of disease vary in inverse proportion to the demonstrated strength of the antitoxin; that after separation of the child, which separation removes the main source of the toxic insult and the antitoxin absorptive power of the child, the rapidity of recession of signs of toxemia tend to vary in direct proportion to the rise of antitoxin strength as occurs in snake venom poisoning, according to the amount and strength of the antitoxin administered; and that the infant may be injured or killed if the antitoxin becomes too strong and attacks the cells of the fetus, whose cells contain the same toxic substance which has demonstrably provoked the antitoxin formation.

The last demand has been adequately satisfied according to this viewpoint by the work of Levine, Katzin, and Burnham, Javert, and many others. As an aside, it may be interesting to know that, pursuing this line of thought, it was argued by analogy and prediction that if the mother's antitoxin could injure or kill her child, one should be able to kill a rattlesnake by the injection of the antitoxin specific to its toxin. Not being able to obtain any information on the subject, this was tried with the aid of Dr. W. J. Breckenridge, director of the Museum of Natural History of the University of Minnesota. After first testing a rattlesnake for serum reaction, a dose of anti-toxin was injected which was deemed adequate to protect a human from the bite of a moderate-sized rattlesnake. In fifteen minutes, every muscle of the snake became convulsed, the snake assumed a cartwheel attitude, snapping convulsively at its vibrating rattles, and, after intervals of apparent recovery, died in eighteen hours.

The cells of the vital organs showed pathology. There was a functional relationship between the size of the snake used, the size of the dose of antitoxin, and the severity of gross reaction and microscopic destruction. This work is being conducted to determine whether, after prolonged administration of sublethal doses of antitoxin, basic lesions would obtain as may obtain in an erythroblastotic child that is ostensibly cured by blood transfusion. It has become a grave question with many whether one is justified in subjecting a mother to whatever danger resides in a cesarean section, to obtain a child that has only a slight chance of life, and, if it is saved, may be cruelly handicapped by basic lesions.

When this serologic exploration was begun in 1919, the findings soon seemed so adverse that it was discontinued. When, in 1923, McQuarrie published his article in corroboration of the theory that incompatibility of blood might be the cause of pregnancy toxemia, his arresting findings were considered due to the element of chance sampling. At that time, of course, the A and B agglutinogens and the anti-A and anti-B agglutinins, considered merely as characteristics but involved in blood incompatibility, were alone envisaged. Under the same conditions, a resumption of investigation showed that for every woman who developed toxemia while bearing an incompatible child, a like case would be found showing no sign of toxemia. It seemed that one need not waste time multiplying these findings by any large figure to come to a conclusion that incompatibility was not likely the cause of toxemia. However, as variants were disclosed, such as: whether the mother, child, or both were or were not secretors; the question of placental integrity; and especially the possibility of viewing agglutinogens as structural parts of basic toxic substances, and agglutinins as one arm of inherited antitoxic substances, the findings took on a different significance and former arguments derived therefrom became fallacies of neglected aspect. If such natural protections could be reasonably assumed, it then would seem highly significant that in 50 per cent of mothers bearing incompatible fetuses, toxemia would be manifest. The most damning evidence against the probability of incompatibility as a factor in the causation of toxemia was afforded by the cases in which no incompatibility could be demonstrated. McQuarrie's findings that toxemia was 16½ times more frequent where incompatibility existed than

where it did not exist could not be duplicated. In fact, there did not appear to be a significant increase of toxemia in those bearing incompatible children when compared with the cases of toxemia in which the children were compatible. From this data it seemed that upon the basis of incompatibility alone the hypothesis was untenable.

Because of this evidence, a maternal intradermal skin test was devised, designed to give evidence, by prediction, that a toxin came from the fetus and that the mother was immunized to this specific toxin. Though the results of this test converged in evidence of the high degree of probability of the hypothesis, the test in no way identified the nature of the suspected toxin, and the test could be made only after the birth of the child.

Then came the discovery of the Rh factor by Landsteiner and Wiener, the disclosure, by Wiener and Peters, of the danger of isoimmunization by this factor in transfusion, and the work of Levine, Katzin and Burnham, showing the relationship of this factor to erythroblastosis fetalis, abortions, stillbirths, and macerated fetuses. This work seemed to complete the whole circle of the classical and largely accepted toxin antitoxin mechanism, enunciated by Ehrlich. In these cases of clinical erythroblastosis the correlation of an accompanying toxemia is about 30 per cent, which is significant, as it is far above the average incidence of toxemia in general from whatever cause. This would seem to logically mark the Rh substance as a toxin when it can gain access to a host not possessing a similar substance by heredity. Furthermore, since antibody studies have been made on suspicion of the possibility of beginning isoimmunization, several of these cases have shown beginning isoimmunization not severe enough to give evidence of fetal injury at birth, and yet some of these mothers have shown clinical evidence of toxemia. Again, from the third case exhibited below, it would seem likely that in the cases of erythroblastosis not showing toxic symptoms in the mother, the antitoxin is so strong that it protects the mother while injuring the child. Philosophically, from what is known about snake venom and bacterial toxemias, it would seem hardly credible that any substance toxic enough to provoke the formation of an antitoxin that could injure or kill the fetus could so function without at any time producing some clinical manifestations of disease in the mother, unless she were thoroughly protected by the antitoxin. Possibly some almost subclinical manifestations are being overlooked.

It soon became evident that the A and B substances could bring about the same train of phenomena when the Rh status of fetus and mother were similar, thus placing these substances under the definitions of toxins. This became increasingly evident when the agglutinin titers were followed both before and after the separation of the fetus.

It seems now that when one can prove from the blood status of husband and wife that the child may inherit one or more of the three substances, A, B, Rh, of a type not possessed by the mother, that woman should be watched with especial care. Even though both mother and child are protected by various proved safeguards, at times, mother, child, or both, may be injured or killed in the toxin-antitoxin battle.

Irregular cross-matching reactions, as well as hiatuses in the fetal toxin evidence of pregnancy toxemia, would indicate that all implicated blood substances have not been found. However, these hiatuses now seem so relatively less frequent that they speak less against a fetal toxin hypothesis and more for either an intensive search for yet unknown blood substances, or for their differential value in diagnosis. Some of these hiatuses may represent true cardiovascular-renal causation, due to vital organ deficiency, either the result of heredity or previous diseases, among which a previous pregnancy toxemia must be included.

Our current accepted forms of pregnancy oversight and treatment have empirically satisfied the therapeutic demands of such a toxin-antitoxin setup: supportive, eliminative, and protective treatment, and separation of the fetus before serious damage has been sustained by mother or infant.

The validity of the main argument is not of mere academic interest. Its main importance lies in the direction that it gives to the possible development of specific antitoxic sera for ready use, in the interests of the mother, either after the intrapartum death of the child or after delivery of a live child, especially in postpartum eclampsia. This direction is being pursued.

Three examples have been chosen for your criticism of the arguments involved. They have been chosen because, no matter what variants are involved, the mechanism seems to stand out clearly. Between the three, all the demands of proof first cited are fulfilled. The mothers were in group O, the husbands in group A, the children in group A, and mothers, husbands, and children were Rh positive. The common denominators, it was felt, permitted a more accurate comparison and interpretation.

Case Reports

Case 1.—A primigravida. With the accession of manifestations of toxemia, her anti-A agglutinin titer had risen to around $\frac{1}{1,000}$. Her anti-B titer did not rise. It was clinically a low grade toxemia, but required hospitalization around the thirty-fourth week because of a brisk hemorrhage with pain. The condition was checked by pelvic examination and soft tissue roentgenograms, and diagnosed as a minor premature separation, which was later corroborated upon the birth of the child. The bleeding and pain quickly ceased and, with slightly increasing manifestations of toxemia, she delivered normally at term a clinically and serologically normal group A child. Five days post partum, the mother's anti-A agglutinin titer rose to around $\frac{1}{2,000}$, and she made a slow recovery.

Here would seem to be an example of a group O mother reacting to an A toxin by the formation of additional antitoxin. Her inherited complement of antitoxin was not sufficient to protect her fully from manifestations of toxemia, nor was it ever strong enough to demonstrably injure the child. The minor increase in the strength of the antitoxin after the birth of the child with its antigen insulting and antitoxin absorptive powers, allowed of only a slow recovery from the manifestations of toxemia.

Case 2.—A primigravida developed a toxemia accompanied by an anti-A agglutinin titer around $\frac{1}{1,000}$. This titer did not increase with increasing manifestations of toxemia. About the twenty-eighth week, the child died in utero, and was delivered. Five days post partum, the mother's anti-A agglutinin titer rose to $\frac{1}{100,000}$, with a rapid disappearance of toxic manifestations.

Here a reasonable interpretation would seem to be that the antepartum antitoxin strength was kept low by fetal antibody absorption. The latter, in conjunction with marked placental infarction at the front line of the toxin antitoxin battle, likely killed the fetus. As soon as the mother's antitoxin was given a chance to accumulate, her toxic manifestations melted away rapidly. The same course and pattern evokes when one gives rattlesnake antivenom in rattlesnake poisoning.

CASE 3.—A multigravida who gave a history of two previous erythroblastotic disasters. Her anti-A agglutinin titer rose to around $\frac{1}{8,000}$. No signs of toxemia were obtained, or at least they were not noted. At the age of estimated viability of the fetus, the mother was delivered by cesarean section of an erythroblastotic child, whose immediate life was saved and whose manifest severe lesions disappeared under multiple transfusions. Five days after delivery the maternal anti-A agglutinin titer shot up to $\frac{1}{8,000,000}$ plus. She made an uneventful recovery.

Here we seem to have an example of an antitoxin level that apparently protected the mother but was held deceptively low by the antitoxin absorptive power of the fetus. After separation of the fetus, the true strength of the antitoxin formative power of the maternal cells made itself manifest both by the lesions in the child and by the tremendous increase in the antitoxin titer in the mother.

Conclusions

In closing, may it be said that the routine knowledge of the A, B, and Rh status of husband and wife has been found to be of more frequent use and of as great value as the routine knowledge of the Wassermann status. As both may be obtained with one drawing of blood, nothing is added to the inconvenience of wife or husband. It gives one a reasoned feeling of security, or at least of preparedness in facing the problems that may ensue. It permits the more accurate segregation of cases that bear special watching. It permits one to be more sure of the matings that will not likely result in toxemia of pregnancy, premature separation of the normally implanted placenta, or fetal injury, death, and abortion due to a toxin-antitoxin mechanism. It permits the building up of available sources of Rh-negative blood of every group to which one may turn in case of need in the interests of mother or child.

Far from engendering unnecessary anxiety, experience proves that the procedure is very reassuring to all concerned. It is amazing how widespread has been the dread aroused in men and women alike, by the articles in the public press and magazines concerning the Rh factor. Men and women alike express relief that their genetic status is being kept in mind, and cooperate enthusiastically in having the tests made. Whatever the findings, one is enabled to quiet inordinate fears and make the patients realize the extreme infrequence of the dire results that they envisage. Where, before, they often resented the implications of the Wassermann, and, now and then the husbands succeeded in avoiding the test, all welcome the genetic test, and as all the tests may be made from one drawing of blood, the Wassermann test need not be mentioned.

Discussion

DR. J. P. PRATT, Detroit, Mich.—Nearly 50 years ago Zweifel designated eclampsia as "the disease of theories." Presentation of a new theory today indicates that we are

still groping for facts and that our knowledge regarding toxemia remains immature. Early theories referred to disorders of the nervous system peculiar to pregnancy. Other early theories referred to bacterial invasion. Williams, in 1903, summarized as follows: "The clinical history and anatomic findings afford presumptive evidence that the disease is due to the circulation of some poisonous substance in the blood which gives rise to thrombosis in many of the smaller vessels, with consequent degenerative and necrotic changes in the various organs. But, at the same time, we are absolutely ignorant concerning the nature of the offending substance, and besides, the experimental evidence thus far adduced in favor of such an etiologic factor is not convincing." Since then advances in metabolic and endocrine studies as well as the discovery of blood groups have stimulated many new theories.

A new proposition is welcome inasmuch as no theory yet proposed adequately explains eclampsia. When no experimental data has been presented, perhaps the best way to establish the value of a theory is to ask questions about it. May I ask how the author justifies using agglutinogens and toxins synonymously? By definition: an agglutinogen is any substance which, acting as an antigen, stimulates the production of agglutinin, while a toxin is any poisonous substance of microbic, vegetable, or animal origin which does not cause symptoms of poisoning until after a period of incubation and are antigenic. It seems illogical to use these terms interchangeably, implying that red cells and their agglutinogens are actually poisonous. Further, these agglutinogens do not satisfy the definition of a toxin, as a reaction to them is immediate rather than after a period of incubation. The clinical and pathologic manifestations of toxemia and transfusion reactions are not similar.

The higher incidence of eclampsia with hydatidiform mole indicates that the offending object is the chorion but not the fetus. Incompatibility of the elements of the blood is not possible in such cases for there is only one source for all the blood.

If toxemias are due to hereditary incompatibiliay of blood of mother and fetus, can this change to compatibility during pregnancy? If not, what explains the improvement in toxemias when given proper prenatal care?

One can heartily agree with the advice to study blood grouping of all prenatal cases, including the husband's whenever possible.

DR. HERMAN W. JOHNSON, Houston, Texas.—Dr. LaVake indicates that there might be some connection between the different blood groups, and especially the Rh factor, of fetus and mother, as an etiologic factor in toxemia. It's an interesting speculation, but offhand one regrets to have the present confusion surrounding the toxemias further complicated by the confusion of the Rh factor. The theory of antagonistic blood groups as an etiologic factor was exploded early in this century. If now the Rh factor has to be investigated there would be slight hopes that it would offer any solution. Naturally it would have to depend on the antigen-agglutinin reactions with all its possibilities. If that were the case, it would be logical to expect the pattern of erythroblastosis to be followed, in which event a sensitized mother would suffer a more severe toxemia with succeeding pregnancies which is not the case, as every clinician knows.

Dr. Pratt has just suggested that we do not know much more about the etiology of eclampsia than we did years ago. I know we do but also know that many of us refuse to accept the known facts. It is known that eclampsia occurs only in the human female, who is the only animal which maintains the upright position. Therefore there is some connection between the venous back pressure of the upright position and eclampsia, and especially when this is combined with primigravida, oversize babies, twins, and polyhydramnios. We know that a placenta has to be present in order to have eclampsia. And in postpartum eclampsia there is a symptom continuity of hypertension from shortly after the expulsion of the placenta up to the time of the convulsion. It is quite safe to say that eclamptic toxemia is impossible either in late hydatidiform mole or in late pregnancy without marked degeneration of chorionic epithelium. In both instances the chorionic epithelium has been deprived of much of its blood supply. We know that there is a circulating toxin in eclampsia. (We have made quantitative determinations of the tyramine in the blood of eclamptics, and we feel that other

toxic amines may be formed from their respective amino acids in the degenerated chorionic epithelium.) It is well known that there is no longer any place for Welch's "Dictum" in the postmortem finding of eclampsia. These findings are identical with death from toxins and poisons. It is easy to say eclampsia is a disease of theories. Why not check and recheck the things which are known?

DR. LAVAKE (Closing).—Dr. Johnson has answered Dr. Pratt's question regarding hydatidiform mole and pregnancy toxemia.

Dr. Pratt asks how one can associate an agglutinogen with a toxin. The realization of such an association has been just as difficult for me to reach as it is difficult for you, because we have all been raised on the same traditional ideas and canons of serology as they pertain to blood groups and blood transfusion. Here, their original brilliance remains undiminished. But they were formulated to meet the demands for a logical explanation for the phenomena resulting from the gross mixture of bloods, a purely artificial procedure.

Though Hopkins, in 1910, and Ottenberg and Kaliski, in 1913, showed that incompatible blood was not only agglutinated by the blood of the recipient, but was hemolyzed, and the red cells devoured by the leucocytes of the recipient, we have always felt called upon to attribute the phenomena not to an antitoxin, as in bacteriology, but to some special properties in blood—a different mechanism, as it were. Now, the findings in maternal toxemia and erythroblastosis fetalis suggest clearly that a toxin-antitoxin relationship here exists between fetus and mother, depending upon differences in cell substances. The agglutinogens stem from these cell substances and thus are associated with toxic substances under the conditions that make the substances toxic to other cells.

It has been asked why, if this be true, we see less toxemia now than formerly. Experience would suggest that this is due to more widespread and better prenatal care, the elimination of focal infections, attention to the prevention of general infections, and more early and intensive treatment: but, experience would add that it is significant that some of the worst toxemias obtain in spite of the earliest recognition and the best treatment.

In answer to the query as to how one can associate an isoagglutinin with an antitoxin when the former is rapid in action and the latter shows a delayed action, it may be said that if one follows isoagglutinin titers following a sublethal injection of incompatible blood, it will be found that it takes about twelve days for the specific isoagglutinin titer to reach its height. It follows the pattern of antitoxin rise in bacterial infection. The rise of the agglutinin titer is one of the indices of the rise of antitoxin strength because it is one of the functional arms of the antitoxin.

THE Rh FACTOR IN ABORTION*

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IN THE literature on the clinical importance of the Rh factor there are many intimations that this factor in the blood is a relatively common cause of abortion. However, only Schwartz and Levine and Javert discussed this possibility in detail. Levine noted that the blood of only one in nine women who had experienced two or more spontaneous abortions was Rh negative. Javert studied twelve cases of habitual abortion (number of pregnancies not stated) and found the blood of nine (75 per cent) of the women concerned to be Rh positive. He concluded that "unless additional evidence shows the contrary, early habitual abortions should not be attributed to (Rh factor) iso-immunization."

Previous Work

In January, 1945, I reported results of a preliminary study carried out to determine whether or not the Rh factor seemed commonly involved in the etiology of recurrent abortion and miscarriage.† Twenty-five cases were collected over a period of two and a half years. In 22 (88 per cent) of these the blood contained the Rh factor, and in three (12 per cent) the blood did not contain this factor. Since the percentage of women whose blood did contain this factor was as large as that in the general population, it was tentatively concluded that etiologic influences other than the Rh factor had been in effect to produce these instances of repeated abortion.

The Present Study

Frequency of True Recurrent Abortion.—The study to be reported now is an expanded one, similar in nature to the one just cited. It consists of a group of 93 women afflicted not only with recurrent abortion, but also with repeated miscarriage. Among these 93 women with recurrent abortion there were also a few instances of stillbirth and neonatal deaths. The patients represent, in so far as was possible, all such patients coming to the Mayo Clinic whose blood was tested for the Rh factor, who were pregnant and had such a history of recurrent abortion, or who were not pregnant but presented themselves with the primary or secondary complaint of repeated abortion or miscarriage. During the four years in which this series was collected there were approximately 75,000 women admitted to the clinic between the ages of 20 to 40 years. Hence, it will be seen that true recurrent abortion is not a very common condition. Table I represents the obstetric histories of these women as a group.

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*Read, by invitation, at the Fifty-Seventh Annual Meeting of the American Association of Obstetricians, Gynecologists, and Abdominal Surgeons at Hot Springs, Va., Sept. 5, 6 and 7, 1946.

†The terms "abortion" and "miscarriage" as used in this paper are based on the definitions given in Stander's text; that is, an abortion is a pregnancy which terminates before sixteen weeks' gestation; a miscarriage is a pregnancy which terminates between the sixteenth and twenty-eighth week of pregnancy.

TABLE I. SUMMARY: OBSTETRIC HISTORY: 93 PATIENTS, PREGNANT 362 TIMES, WITH RECURRENT ABORTION AND MISCARRIAGE

CONDITION OR RESULT		PREGNANCIES	PER CENT
Abortions		235	64.9
Miscarriages		69	19.1
Premature stillbirths		10	
Premature neonatal deaths		4	5.2
Term stillbirths		3	
Term neonatal deaths		2	
Live children			
Term	33		
Premature	6		10.8
Total pregnancies		362	100.0
Pregnancies with no living children		323	89.2
Pregnancies resulting in living children		39	10.8

TABLE II. THE RH FACTOR IN 93 CASES OF RECURRENT ABORTION AND MISCARRIAGE

RH FACTOR	PATIENTS	PER CENT
Present	76	81.7
Absent	17	18.3
Total	93	100.0

Frequency of Rh Factor.—In Table II it is revealed that the blood of 17, or 18.3 per cent, of the 93 patients did not contain the Rh factor. This is somewhat higher than the 15 per cent of women in the general population whose blood does not have the factor, and is higher than that which has been observed among women patients routinely seen by obstetricians and gynecologists of the Mayo Clinic.

TABLE III. THE RH FACTOR IN 34 CASES OF TRUE HABITUAL ABORTION (THREE OR MORE SPONTANEOUS ABORTIONS OR MISCARRIAGES WITH NO LIVING CHILDREN)

RH FACTOR	PATIENTS	PER CENT
Present	27	79.4
Absent	7	20.6
Total	34	100.0

If one corrects for the fact that the blood of two of the husbands of the seven women not having the factor similarly did not have the factor, then five, or 14.7 per cent, of the 34 women in this series could possibly be affected by the Rh factor. (These were the only husbands whose blood was tested in the group of women whose blood did not have the Rh factor.)

Also, the data in Table III point to some decrease in the occurrence of the Rh factor among women who have what is usually more rigidly defined as "true habitual abortion," as shown by the blood of 34 patients (in the series of 93) afflicted with this condition. The blood of seven of 34 patients, or 20.6 per cent, proved not to have the Rh factor. The blood of two of the husbands of the seven women who did not have this factor was tested and found not to contain the Rh factor. Thus, only five, or 14.7 per cent, of the 34 couples under consideration could have been involved by the Rh factor (woman not having the factor, husband having the factor). The percentage is slightly higher than that in the general population, since about 12 per cent of marriages involve women whose blood does not contain the factor with men whose blood does. However,

there were only 93 cases in the total series, and we should hesitate to generalize on the basis of so small a series. Moreover, it must be emphasized that this series is concerned only with recurrent persistent abortions. It may be noteworthy to remark that no proved instance of erythroblastosis was noted in the histories of these 93 patients, nor at their subsequent delivery in the Section on Obstetrics and Gynecology of the Mayo Clinic. One case, in review, probably involved erythroblastosis, and the histories of two other patients are suggestive. Of course, many of these histories extend back well before 1940 and our exact knowledge of the Rh factor.

TABLE IV. PRESENCE OR ABSENCE OF RH FACTOR AMONG 25 PATIENTS WHO HAD ONE NORMAL LIVE BIRTH FOLLOWED BY A SERIES OF NONPRODUCTIVE PREGNANCIES, MISCARRIAGE, STILLBIRTH, ETC.

ONE LIVE BIRTH FOLLOWED BY	RH FACTOR, PATIENTS	
	PRESENT NUMBER	ABSENT NUMBER
Two nonproductive pregnancies	8	0
Three nonproductive pregnancies	5	2
Four nonproductive pregnancies	8	0
Five nonproductive pregnancies	2	0
Totals	23	2
Percentages	92	8

Possible Effect of Rh Factor After One Normal Delivery.—Table IV concerns a subgroup of the 93 patients who had recurrent abortion and miscarriage. This subgroup is composed of 25 patients who first had a normal living child and then were pregnant two or more times, each time nonproductively. Members of this group presented a type of obstetric history that could often, by reason of its sequence of events, theoretically be attributed to the action of incompatibilities of the Rh factor. It will be noted that the percentage of women who did not have the Rh factor is less than that observed in the general population.

Frequency of Abortion, After Erythroblastosis Fetalis, in Women Affected by the Rh Factor.—The problem of the Rh factor as it influences abortion can be viewed in a reverse light; namely, do women who are affected by the Rh factor to the point of delivering erythroblastotic fetuses experience abortion with any greater frequency than women not thus affected?

In Table V is revealed our experience with this type of patient in the two years prior to the time of this report. The table shows no evidence of abortion or early miscarriage in this very small series of 13 patients. Only seven pregnancies in Table V are those subsequent to the birth of infants who had erythroblastosis. Because these data are far too small to be at all conclusive,

TABLE V. SUMMARY: OBSTETRIC HISTORIES: 13 PATIENTS DELIVERED OF 20 ERYTHROBLASTOTIC FETUSES IN 43 PREGNANCIES*

TERMINATION OF PREGNANCY AT	NUMBER OF PREGNANCIES
Under six months' gestation	0
Six to eight months' gestation	6
Eight months' gestation or more	37
Total pregnancies	43

*Seven infants were stillborn or died in a few minutes, and their condition was assigned a definite or presumptive diagnosis of "erythroblastosis fetalis."

resort was made to the tables of obstetric histories of 44 women whose blood did not contain the Rh factor and who bore infants with erythroblastosis, as published by Race, Taylor, Cappell, and McFarlane.

The data in Table VI point to no increase in the frequency of abortion in pregnancies after involvement by erythroblastosis fetalis. It may yet be too soon to determine this point. Javert wrote that iso-immunization by the Rh factor may increase the early termination of pregnancy by as much as 32 per cent.

TABLE VI. OBSTETRIC HISTORIES OF 44 WOMEN (178 PREGNANCIES) WITHOUT THE RH FACTOR WHO BORE ONE OR MORE INFANTS WITH ERYTHROBLASTOSIS*

OUTCOME OF PREGNANCIES	PREGNANCIES BEFORE DIAGNOSIS OF ERYTHROBLASTOSIS FETALIS		PREGNANCIES AT WHICH DIAGNOSIS OF ERYTHROBLASTOSIS FETALIS WAS MADE	PREGNANCIES AFTER DIAGNOSIS OF ERYTHROBLASTOSIS FETALIS	
	NUMBER	PER CENT†	NUMBER	NUMBER	PER CENT‡
Living children	82	75.9	12	6	23.1
Stillbirths	11	10.2	3	2	7.7
Neonatal deaths	7	6.5	29	15	57.7
Abortions	5	4.6	0	0	
Miscarriages	3	2.8	0	3	11.5
Totals	108	100.0	45§	26	100.0

*Modified from Race, R. R., Taylor, G. L., Cappell, D. F. and McFarlane, M. H.: Rh factor and erythroblastosis fetalis; investigation of 50 families, Brit. M. J. 2: 289-293 (Sept. 4), 1943.

†Of 108 pregnancies.

‡Of 26 pregnancies.

§One set of twins.

Abortion Among Women Who Do and Do Not Have Rh Factor.—Another way of appraising the influence of the Rh factor in abortion, especially in casual ordinary abortion as contrasted to recurrent abortion, is by review of the incidence of abortion in a sizable group of women who do not have the Rh factor, as compared with the incidence in a control group of randomly or consecutively selected women who do have the Rh factor.

In Table VII are presented such data. They confirm the assumption that so far as stillbirths and neonatal deaths are concerned, absence of the Rh

TABLE VII. RESULTS OF PREGNANCY AMONG 228 WOMEN WHO DID NOT HAVE RH FACTOR AND 228 WOMEN WHO DID HAVE RH FACTOR

PREGNANCIES AND RESULTS	RH FACTOR			
	ABSENT, WOMEN		PRESENT, WOMEN	
	NUMBER*	PER CENT†	NUMBER*	PER CENT‡
Living children	313	83.0	277	83.2
Ectopic pregnancies	4	1.1	3	0.9
Abortions, all	31	8.2	37	11.1
Miscarriages	5	1.3	11	3.3
Stillbirths	17	4.5	3	0.9
Neonatal deaths	7	1.9	2	0.6
Total pregnancies	377	100.0	333	100.0

*Of pregnancies or conditions noted; not number of patients.

†Of 377 pregnancies.

‡Of 333 pregnancies.

factor is a definite hazard, because the incidence of these two casualties of pregnancy was 6.4 per cent among women who did not have the factor, whereas in the control series of women who did have this factor, the incidence was only 1.5 per cent. There is no similar evidence that absence of the Rh factor is an important cause in the production of *early* casualty of pregnancy. For neither abortion nor miscarriage was the rate of occurrence greater among those women who did not have the Rh factor than among those who did. In fact, in these two series, each composed of 228 women, there were actually fewer abortions and miscarriages (9.5 per cent) among women who did not have the factor than among women who did have the factor (14.4 per cent). Hence, we must hold in abeyance any opinion that the Rh factor is an important cause of abortions and miscarriages, as these two casualties of pregnancy ordinarily are encountered. If absence of the Rh factor has a part in the causation of abortion, it is overshadowed, so to speak, by other causes, and is not apparent statistically. As I have suggested previously herein, the situation is somewhat different in respect to persistent abortion.

Comment

If an abortion is caused by the results of iso-immunization by the Rh factor, it would seem logical to expect to find anti-Rh agglutinins in the mother's blood early in pregnancy, in the blood of at least some of the women tested, and in a significant titer. Reports of such findings have not yet been published. In the few cases in which we have carried out such tests to date, anti-Rh agglutinins have not been found. Vaux and Rakoff have reported that the results of such tests of the blood of two women subject to habitual abortion were negative. The Rh factor has been demonstrated in the fetal blood as early as the fourth month of gestation by Bornstein and Israel, and also by Kariher and Spindler. It may be that time and further study will justly implicate the Rh factor in the cause of spontaneous interruptions of early pregnancy in some cases. However, the facts that the blood of a woman subject to habitual abortion does not contain the Rh factor, and that such a woman is married to a husband whose blood does contain the factor, should in no way call forth the opinion that the prognosis for her pregnancy is poor. She is still entitled to the usual investigation and therapy that are extended to any group of relatively infertile patients, and her chances for successful termination of pregnancy are worth an effort on the part of her obstetrician.

The Rh factor is carried chiefly in the erythrocytes. The total fetal cell volume early in pregnancy must be small. In other words, the volume of the Rh antigen is too small to be able to influence the mother until at least mid-pregnancy. Theoretically, this may explain the discrepancy noted in Table VII between the effect exerted by the Rh factor on casualties of *late* pregnancy compared with those of *early* pregnancy.

Conclusions

Casual or ordinary abortion seems uninfluenced by the mechanism of the Rh factor. The incidence of stillbirth and neonatal deaths, however, is higher

among women who do not possess the Rh factor than among those who do. When recurrent abortion and miscarriage are considered, however, the number of women in a group of 93 whose blood did not contain the Rh factor was somewhat higher, comparatively, than would be true in the general population. Conversely, on the basis of the data analyzed, there seems to be no striking increase in the frequency of occurrence of abortion or miscarriage after maternal involvement by the Rh factor as evidenced by the occurrence of erythroblastosis fetalis. On the other hand, there is a striking increase in the casualties of late pregnancy among women whose blood does not contain the Rh factor. Data concerning a small series of 25 women who gave birth to a normal child and then began to experience abortions and miscarriages were analyzed. In this series there were fewer women whose blood did not contain the Rh factor than are found, comparatively speaking, in the general population.

The Rh factor possibly has been overemphasized as a cause of abortion and miscarriage at the expense of more common causes, such as dysfunction of the ovaries, pituitary body, thyroid glands, and possibly the testes of the husband. A woman subject to habitual abortion whose blood does not contain the Rh factor deserves a chance to attempt another pregnancy under the more nearly ideal physiologic environment than proper therapy may provide.

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Discussion

DR. FREDERICK H. FALLS, Chicago, Ill.—Whenever a discovery is made in the practice of medicine, whether it be diagnostic or therapeutic, we can be assured that false as well as true assertions will prevail about its action until sufficient time will have elapsed for critical evaluation of the claims made concerning its action by the earlier workers in the field. Dr. Hunt has tested out the claim that the Rh factor is an important cause in the production of casual and habitual abortion and found it wanting. The data he presents show without doubt that in this series there is no evidence that the Rh factor had any important part to play in the causation of abortion. The weakness of a study such as this lies in the relatively small number of cases which, as Dr. Hunt rightly points out, renders the statistical value of only relative importance. However, because it is difficult now and has been more difficult because of war conditions and because of the scarcity of the antigen in the early years of the discovery of the Rh factor, it is necessary for various clinics to supply information on their experience which, when pooled with that of other clinics, will give us the answer we are seeking.

Our experience with habitual and casual abortion has led us to the belief that in most cases the cause of the abortion was due to anatomic or endocrinologic defects which when corrected resulted in a very favorable effect on the tendency to abort. If the Rh factor

had been an important contributing factor we should have failed to get the response which we did get when we corrected these anatomic and endocrine factors in a larger percentage of cases.

I should like to emphasize what Dr. Hunt has pointed out, that it is highly improbable that enough of the Rh factor would be likely to get from the fetal to the maternal circulation in the early stages of pregnancy to have a serious significance in the causation of early abortion, since the factor is carried by the red cells.

In the later months, in normal as well as pathologic cases, the vascular accidents in the placenta, infarct formation, and degenerative changes may well lend themselves to destruction of fetal red cells and absorption by the mother of the antigen, or the transfer of whole cells into the maternal blood stream. This would result possibly in producing circumstances that would lead to premature labor or erythroblastosis, but not habitual abortion.

We have analyzed routinely 615 cases with only 38, or 6.1 per cent, Rh negative. If we had had 1,000 cases the figures might be more comparable to those found in the general population.

RH FACTOR DETERMINATIONS—615 CASES
(FEBRUARY 22, 1946, TO AUGUST 31, 1946)

	NUMBER	PER CENT
1. Rh-negative women	38	6.1
2. Rh-negative women with Rh-positive husbands	16	
3. Rh-negative women who came to the clinic for abortion or miscarriage	1	
4. Abortions or miscarriages which were uncomplicated by Rh considerations. (Taken from a survey of 100 Rh-positive multiparas)	25	25.0

RH-NEGATIVE WOMEN WITH RH-POSITIVE HUSBANDS—16 CASES

	NUMBER	PER CENT
1. Rh-negative women with Rh-positive husbands who have a history of habitual abortions or miscarriages	5	31.2
2. Rh-negative women with Rh-positive husbands uncomplicated by abortions or miscarriages:		
A. Primiparas (undelivered*)	4	25.0
B. Multiparas	7	43.7

*It is difficult to evaluate the primiparas since we do not know the prognosis of their gestation, but they had passed the fourth month of pregnancy.

It would seem, therefore, that our figures corroborate the findings of Dr. Hunt, although too small in number to be statistically significant. In the light of these findings it would seem proper to encourage Rh-negative women with Rh-positive husbands to become pregnant in the belief that they have not much more than the ordinary risk to run from abortion, and that we should focus our attention on the management of other causes of abortion in such cases that present themselves with a history of habitual or recurrent abortions.

RED DEGENERATION OF UTERINE MYOMAS*

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RED, or carneous, degeneration of uterine myomas was first described by Gebhard[1] in 1899. Probably this type of degeneration was known before, but an accurate description is lost in the early classification of myomas as either "soft" or "hard" without much separation of specific types within that general classification.

In 1903 Fairbairn[2] of England reported 19 of these tumors and presented a complete description of their clinical characteristics and pathology. In 1910 a valuable contribution was made by Murray,[3] pointing out the possible hemolyzing effect of the lipoids in red myomas to explain their color. In 1913 a very specific pathologic classification was made by Smith and Shaw.[4] They divided these tumors into two groups, those in which thromboses were found in the vessels within the tumor, and a smaller group in which the coloration was looked upon as being the result of spontaneous hemolysis and diffusion. Haultain[5] also, in an article for an English system of gynecology, theorized about the type of vascular accident which causes this degeneration.

Since the extensive English publications in the early part of the century occasional reports[6, 7] of red myomas, especially as related to pregnancy, appear in the literature, but for the most part the ideas expressed are not much different from those found in earlier publications. The opinion has been frequently recorded that in pregnancy there may be a special toxin to explain the hemolysis. Finally, some individual tumors of this variety have been looked upon as true angiomas.

It would seem that, in general, this degeneration, though unique as degenerations in myomas go, has been made unnecessarily complicated. The purpose of this paper, though none of the ideas are new, is to try to simplify some of the aspects of red degeneration and to present pathologic specimens.

As indicated above, many ideas as to the etiology of this condition have been expressed. In general, one is impressed by the general failure to apply to red myomas the principles of Sampson's[8] work done in 1912 on the blood vessels of the myomatous uterus. In considering the mechanics of this subject, it seems important to talk definitely about arteries and veins of the myoma and not in general about "blood vessels" as is so commonly done. Sampson's injection work, done with gelatin and repeated during the last few years with synthetic liquid latex,[9] makes it plain that the vessels within a myoma inject as arteries, and that veins are concentrated about the periphery of the myoma and, although they may be large, they penetrate the tumor very little or not at all.

*Read at the Fifty-Seventh Annual Meeting of the American Association of Obstetricians, Gynecologists, and Abdominal Surgeons, Hot Springs, Va., Sept. 5 to 7, 1946.

The usual myoma is fed by multiple branches from a vascular arc in the uterus, although one of the vessels supplying it may be larger than the others. In the beginning the blood supply always looks adequate for nourishment of the tumor although, as is well known, myomas vary a great deal in vascularity. Vessels within the tumor, although arteries, are usually thin walled. Anemic infarction of a myoma is practically unknown except as a gradual process manifest in the ordinary hyaline and cystic degeneration of these tumors. These ordinary degenerations indicate a disturbance of greater or lesser degree in the arterial side of the circulation. The tumor lacks for nourishment, therefore muscle cells and bundles break down and may even liquefy. The usual explanation offered for the arterial changes is that the tumor grows or is extruded away from its primary focus faster than proliferation of arteries can follow. Certain it is that the centers of tumors or those points in others farthest from the source of blood supply break down first.

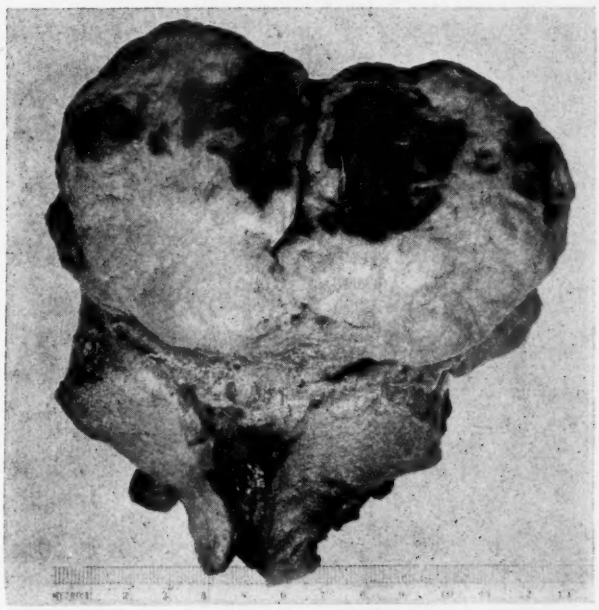

Fig. 1.—Partial and patchy red degeneration of a myoma.

From the clinical behavior of the red myoma, the acute symptoms associated with some, and its gross pathologic appearance, it is evident that this degeneration is a vascular accident, viz., hemorrhage into its substance. Two possibilities exist. The first is primary rupture of vessels within the tumor which are arteries. It would seem that in the full-blown example many ruptures without discernible cause would have to occur at the same time to explain the picture. Although partial or patchy red coloration (Fig. 1) occurs and could be explained on this basis, there is still necessary an explanation for the apparent sudden transformation of a whole myoma nodule, sometimes of a large size, into a tense red tumor. More reasonable, it seems, to look for trouble about the

periphery of the tumor where the concentration of veins exists. Venous obstruction as postulated by Haultain, whether from simple pressure, peripheral thrombosis as seen in some specimens (Figs. 2 and 3), or mechanical injury as seen in one (Fig. 4) appears as a possible cause of the pathologic picture. Blood is pumped into the tumor and cannot get out. The thin-walled arteries of the

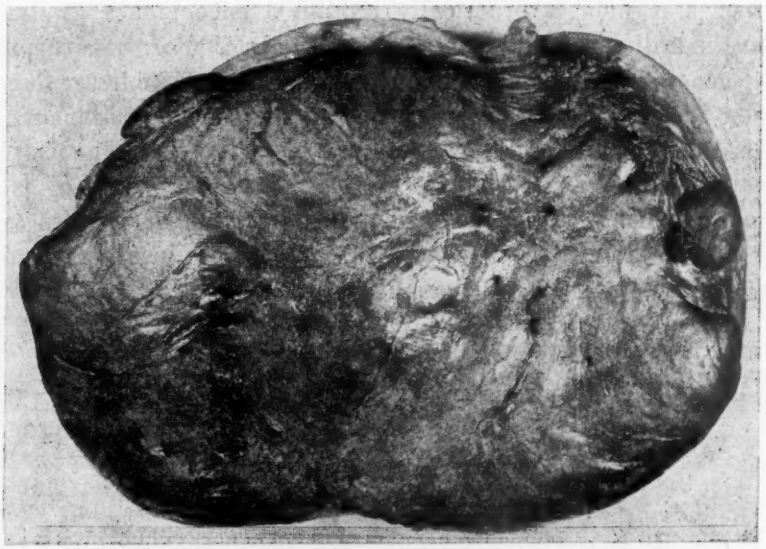

Fig. 2.—Large soft red tumor with peripheral thrombus. Patient had pain, fever, and leucocytosis.

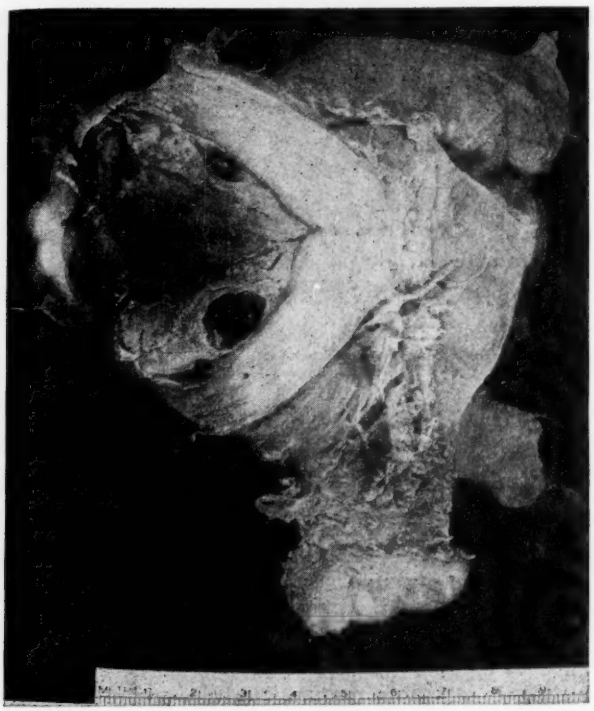

Fig. 3.—Smaller red myoma. No symptoms. Peripheral thrombos.

myoma are ruptured at many points and extravasation of red blood cells occurs (Fig. 5). Such a concept readily explains the rapid swelling of the myoma which has suffered this accident, its tenseness, edema, and the uniform coloration which typical ones present.

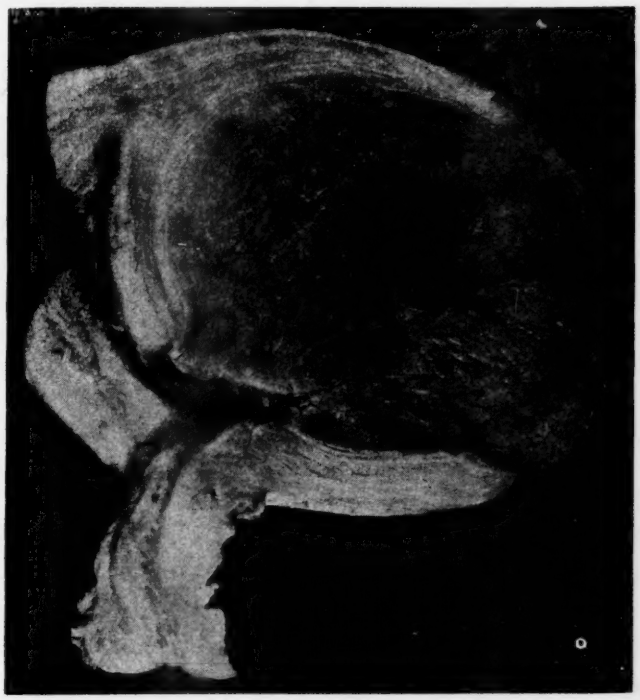

Fig. 4.—Red myoma 9 cm. in diameter when removed two months after an attempted abortion. Peripheral injury.

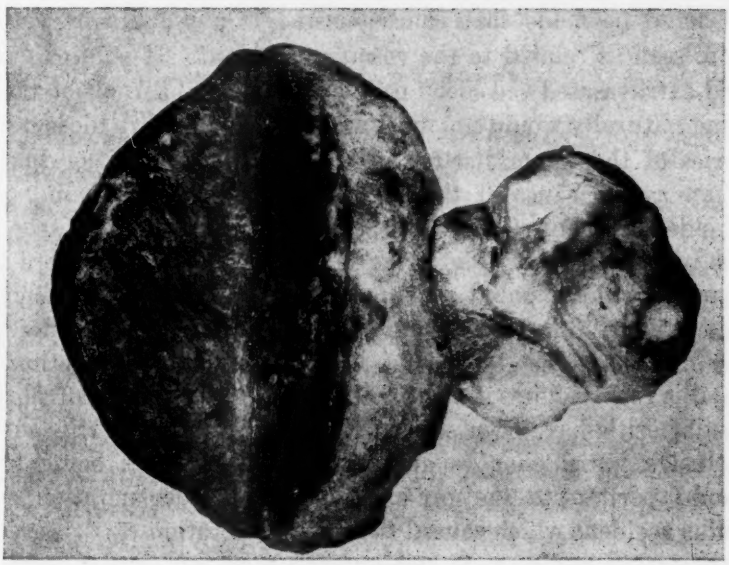

Fig. 5.—A frequent finding in early red degeneration. Thin-walled arteries are engorged with multiple rupture and extravasation of red blood cells.

Although this is believed to be the mechanics of the usual red degeneration, it is apparently certain that a "healthy" myoma will never undergo typical red degeneration, even though hemorrhage occurs within its substance. It would seem that the right degree of hyaline conditioning of the tumor before the vascular accident occurs, is necessary before red blood cells are laked and diffusion of pigment takes place. It is not possible at the present time to refute the idea of Murray[3] that lipoids in the tumor produce the laking, but in many of the tumors studied ordinary fat stains revealed no fat. It is not understood why the ordinary amine cell products of degeneration already present in the myoma which is to be a red one, could not break down red blood cells. On occasion at operation blood has been withdrawn and injected into myomas. The ordinary hard myoma shows no staining except immediately about the needle wound. The softer the myoma, the more diffusion occurs. This experiment is comparable to that of Murray, who immersed pieces of myomas in a hemoglobin solution. Suffice it to say in no myoma has a typical red degeneration been produced. This is understandable probably because a great many small areas of extravasation are present when the accident comes about naturally. It seems possible that the precursor to red degeneration—proper hyalinization—may in addition to changes in chemistry and texture which allow for laking and diffusion, respectively, also make arterial rupture easier when venous obstruction occurs because of loss of firm supporting substance about the vessel walls. Previous hyalinization may govern to some extent the degree of red change. Certainly, firm myomas are frequently seen with large or small hemorrhage into them without general diffuse red transformation.

Much of the complexity of information relating to red myomas arises from the great variety of gross and microscopic features which these tumors present. The point should be made that characteristics of these tumors vary with the time they are seen as related to the vascular accident. If studied early enough it is believed extravasated red blood cells could be found in all of them. Later, such a finding naturally would not exist and, as is well known, does not. Thrombi in the arteries of the tumor itself exist, but if looked upon as due to natural stasis and not as the cause of the degeneration, are to be found only in red myomas of older vintage. Generally speaking, this seems to be true. Thrombi in the veins of the periphery, however, if present at all, are there in recently infarcted tumors, but, as stated above, are not the sole cause of venous obstruction in these tumors. Perhaps even the much discussed presence or absence of demonstrable fat depends on the recentness of the infarction. None of the occasionally reported intrinsic vascular changes consisting of fibrin deposits or actual endarteritis have been seen in the tumors studied. It is surmised that even if occlusive vessel changes are commonly seen that, being arteries, the changes would pertain to the pre-existing hyaline degeneration rather than to the vascular accident which caused the red degeneration.

The point has been made that *typical* red degeneration is seldom seen in twisted pedunculated tumors of connective tissue or smooth muscle, the hemor-

rhage and coloration being more focal in most twisted tumors and lacking the diffuse tinting characteristic of red degeneration (Fig. 6). It is not believed that there is any discrepancy between twisting of a pedunculated tumor and red degeneration, if conditions are similar. The degree of twist should be enough to shut off veins and not arteries, and most particularly the right hyaline conditioning of the tumor before the accident of the twist is necessary if the coloration is to be diffuse.

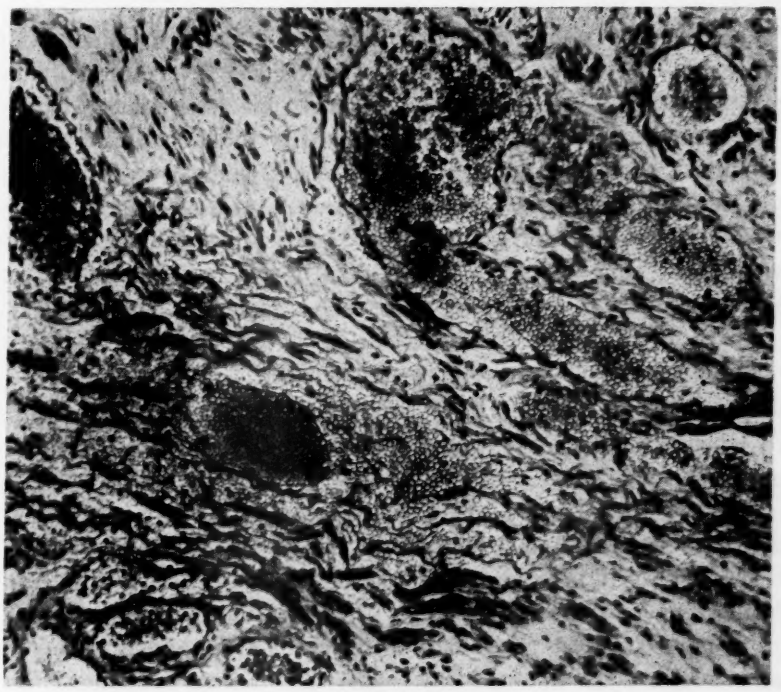

Fig. 6.—Twisted pedunculated myoma. Somewhat more irregular and patchy discoloration than in conventional red degeneration.

After the accident of red degeneration has occurred in a myoma and the stages of acute swelling and extravasation are over, the recovery of the tissue is the same as the recovery from hemorrhage in any structure. Gradually the pain and tenderness of the tumor, undoubtedly caused by the tension within, quiet down, the constitutional signs disappear as the tumor becomes smaller. From observation in a limited number of instances it is believed that a myoma which has suffered the accident of red degeneration may ultimately be even smaller than the original tumor. Infection may occur in these tumors, but it is very rare and usually connected with heavy innoculation from pregnancy or abortion (Fig. 4). Strangely enough, sufficient circulation usually remains or is restored so that complete breakdown and liquefaction of the tumor are rare. The tissues go through the same processes that any black eye or other bruise goes through, and only rarely are any late toxic signs or symptoms discernible in the patient. A curious dryness of some older tumors of this character is common. This is interpreted on the basis of diminution in arterial blood

supply as well as interference with lymphatics about which latter subject little is known as related to myoma. The color of the older dry tumor is likely to be dull brown to slate color, and in some scattered calcification is present. One experience with a large solitary myoma which suffered the accident of red degeneration in the puerperium and was removed by myomectomy several months later, showed a shrunken slate-colored tumor quite dry over the surface and most particularly adherent in its uterine bed. The loose areolar tissue about the myoma was replaced with relatively avascular scar tissue.

The frequency of symptomatic red degeneration in myomas is not great. An incidence of 7 or 8 per cent of all myomas has been handed down as an authentic figure with most occurring, of course, in connection with pregnancy. There is no doubt that when looked for faithfully by the prompt opening of all myomas removed, some degree of hemorrhage and coloration is fairly frequent, even in the nonpregnant uterus. Many tender nodules which are never removed during pregnancy or the puerperium undoubtedly are victims of this change. In our cases, whether pregnant or not, good symptom-producing red myomas have been less than 1 per cent. In these days when myomas in general do not become so large before operation as they used to, it would seem an over-all incidence in pathologic material of 5 per cent is high enough.

With larger myomas which have suffered this accident some patients develop fever and leucocytosis. In the nonpregnant woman, it is doubtful whether the diagnosis of red degeneration can very often be made in small myomas even by reviewing the patient's history after their discovery. Many good small ones are seen which give no symptoms, not being pushed up under the abdominal wall as in pregnancy. All tumors diagnosed before operation in the nonpregnant uterus from signs and symptoms were 10 cm. or more in diameter at the time they were causing trouble. Problems in differential diagnosis occasionally arise. The most common is to determine whether the patient may be suffering from salpingitis rather than from infarction of a myoma. When fever occurs with one of these tumors during the puerperium or the course of an abortion in a myomatous uterus one is faced with the problem of deciding whether puerperal infection is present or not. Rightly placed on the proper aspect of a pregnant uterus, a small red myoma may quite successfully simulate appendicitis.

Since these tumors rarely become infected or completely break down or liquefy, the treatment of them when diagnosis is certain is obvious. Left alone and treated expectantly, especially important in the pregnant uterus, the symptoms quiet down and the tumor shrinks up without too frequent complications. The patient, however, often becomes rather irked at the long-continued discomfort. In the nonpregnant woman, the patient may be treated medically through the acute phases of infarction and surgical treatment carried out with greater ease at a later date. Again it is to be said that such treatment is to be followed only when there is little uncertainty about the diagnosis. One such supposed myoma treated expectantly turned out to be hemorrhage into a granulosa cell tumor. Pedunculated myomas perhaps should not be handled in this way because of the likelihood of twist. Although the process within the

tumor is looked upon as being the same, twisting of the tumor may be associated with greater shock and pain and the arterial supply to the tumor be more interfered with leading to ultimate complete necrosis of tissue.

Summary

Red degeneration of uterine myomas is considered in the light of what is known of the blood vessels of the myoma. It seems clear that red degeneration is a hemorrhagic infarction of a previously hyalinized myoma. Venous obstruction which has to be at the periphery of the tumor is put forth as the vascular accident which best explains this pathologic entity.

It is emphasized that the time the tumor is seen as related to the vascular accident governs the specific pathologic findings.

In the nonpregnant uterus red myomas are usually 10 cm. or more in diameter before there are symptoms or signs enough to make their preoperative diagnosis very certain.

Conservative medical treatment of the acute phases of red degeneration is feasible when the diagnosis is clear and in pregnancy highly desirable.

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Discussion

DR. JAMES R. MILLER, Hartford, Conn.—Dr. Faulkner has reviewed one of the most interesting accidents which occur in the life history of uterine myomas. From his work and from that of Dr. Sampson, it is clear (1) that the blood vessels of myomas are arteries and arterioles and most probably there is a bed of capillaries which empties into veins that are found only at the periphery; (2) that a single nutrient artery is often insufficient to nourish a myoma; and (3) that there is apparently no communication between capillaries and lymphatics in a myoma.

Vascular accidents involving leiomyomas of the intestine give rise to profuse and often fatal hemorrhage, and it may be that they too are supplied only with vessels of the arterial type. They lack the firm capsule which is found in the uterine myoma, and one can readily understand why the picture of infarction or red degeneration is not found, but rather one of uncontrolled and unconfined hemorrhage.

In the minds of some obstetricians who are not familiar with the usual benign course of red degeneration, there may still linger an idea that the painful tumor must be excised lest it grow larger later on in pregnancy, even though the risk of interrupting pregnancy is great. More than one myoma may successively undergo red degeneration as in a patient who is now under my care.

It must be clear by now that a myoma, which presents a sudden painful swelling during pregnancy with leucocytosis and perhaps some elevation of the blood sedimentation rate but

without fever and with or without signs of threatened interruption of pregnancy, presents no indication per se for myomectomy once the correct diagnosis is made.

I have observed that the irritability of the uterus appears to be controlled satisfactorily within twenty-four to forty-eight hours by the intravenous or intramuscular injection of lutein (Hynson and Westcott) even after opiates and rest in bed have failed. When dealing with a patient whose obstetric future is not bright by reason of advanced age or simply because of multiple fibroids, every means should be taken to avoid operation. Myomectomy, of course, can be done without interrupting pregnancy probably safer in the first trimester, though the danger is real and the operation is seldom necessary.

In reviewing some of the specimens which have been removed at cesarean section at the Hartford Hospital, I was impressed with the fact that sometimes no history of a preceding attack could be elicited in a case which presented typical red degeneration. I was also impressed with the innocuous appearance of hyalin degeneration which a fibroid can assume within three or four months after a severe attack of red degeneration which had been sufficient to threaten interruption for many weeks. The appearance of the tumor whether red, brown, slaty grey, yellow, or even with calcification depends on the time following the vascular accident.

CONSERVATIVE TREATMENT AND THERAPEUTIC TEST FOR ENDOMETRIOSIS BY ANDROGENS*

JOHN COOKE HIRST, M.D., F.A.C.S., PHILADELPHIA, PA.

FROM observations beginning in 1942,[1] we can state that androgen will not cure "external" endometriosis, exerts relatively little regressive effect upon hard infiltrates or fused masses as compared to cystic endometriomas, and, apart from the menopausal period, has but temporary action. Also, it may induce arrhenomimetic symptoms, which are always objectionable, possibly serious and permanent,[2] but, except from heavy prolonged dosage, are not inevitable and may be mild.

Notwithstanding the above, aside from relation to endometriosis, androgen has both negative and positive values. Unlike estrogen, it is neither experimentally[3] nor clinically fibromatogenic or carcinomatogenic,[3a, 4] but rather antigenic in these respects, particularly versus inception of mammary cancer.[5] It has positive value in spasmodic dysmenorrhea and mastalgia, less value in premenstrual tension[6] and "functional uterine bleeding,"[7] although not comparable to estrogen[2, 8] for the latter condition. Androgen also exhibits a "tonic" effect approaching euphoria notably at the menopause, when other favorable action may be prominent.[9, 10]

In relation to endometriosis, androgen has also both negative and positive values. Unlike estrogen, it will not reactivate the disease after the menopause,[11, 12] and, according to two of our cases, will not cause regression of cystic ovaries associated with peri-oophoritis and excessive bleeding. Although androgen has been used for acute pelvic inflammatory disease to suppress menstruation, we have not seen regression of inflammatory residues, and therefore suggest the last two negative observations as diagnostic possibilities.

The positive values of androgen, particularly in rapid reduction of pain, tenderness, and swelling of grossly cystic ovarian endometriomas, will be described in 19 brief case reports under diagnostic, therapeutic, preoperative, and postoperative headings, not including a larger number of early nodular cul-de-sac endometriosis with minor symptoms.

Contrary to original intention, only inconclusive haphazard endometrial biopsies and vaginal smears were obtained and no hormonal assays[13, 14] so that nothing new can be presented as to etiology of the disease or biologic action of androgen. However, the rapidity of effect suggests a direct antagonism of androgen versus estrogen, in addition to known reduction of urinary gonadotropic hormone excretion, as indicated in two previous reports.[1, 15]

We have had no experience with the sterol desoxycorticosterone acetate, and no conclusive effect with progestin, each of which should theoretically

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have some effect upon endometriosis,[16] and we have had no opportunity to use androgen preoperatively for adenomyoma or adenomyosis.

Our method of administration has consisted mostly of 150 to 225 mg. of testosterone propionate in oil injected intramuscularly over a period of two to three weeks, followed by 10 mg. daily of methyl testosterone orally for variable periods up to three or more years in three patients, rather than the much less expensive but less controllable pellet implant method.[17] Other than slight virilism and occasional acne, reactions have been negligible.

Case Reports

Diagnosis.—Negative effect upon polycystic ovaries and inflammatory residues was mentioned. In addition to the two cases below, most of the following 17 cases may also be taken as diagnostic.

CASE 1.—(C. T.), single, 36 years of age, abdominal pain after bowel movement for two years, dysuria (hematuria × 1) for four weeks; posterior uterus, stenotic cervix, myoma, cul-de-sac endometriosis. Treatment: dysuria relieved, cul-de-sac insensitive, bowel pain persists. Suspected large bowel endometriosis disproved via testosterone proved to be proctitis.

CASE 2.—(R. U.), married, 23 years old, infertile, acquired right lower quadrant pain with menses, not relieved by appendectomy; posterior uterus; husband sterile. Three years later, acute peritonitis, cause ? Painful menses, large left ovarian cyst, improved with treatment, but operation preferred; pelvic endometriosis and chocolate cyst confirmed, latter removed. Recurrent pain relieved by testosterone.

CASE 3.—*Conservative Treatment.*—Reported in 1943, a case of seven-year sterility, excision of right chocolate cyst, uterine suspension, delivery. Has taken 10 mg. methyl testosterone daily since October, 1942, with no increase in left ovarian endometrioma and no unfavorable manifestations except slight hirsutism.

CASE 4.—Also reported in 1943; first operation, removal of large ruptured right ovarian endometrial cyst; removal of extremely large left ovarian chocolate cyst refused, but opened and drained at second operation for intestinal obstruction. Has taken 10 mg. or more of methyl testosterone daily since May, 1942, with incomplete but marked regression of tumor, relief of pain, and semiobstructive symptoms, and only slight voice change, hirsutism, and vulvar hypertrophy.

CASE 5.—(R. S. C.), married, 36 years of age, has one child; recent menstrual pain, nausea, distention; appendectomy in 1940, adnexa found "O.K." Unrelieved by Elliott vaginal heat; operation: right salpingo-oophorectomy for "tubo-ovarian abscess." Marked regression of secondary large left ovarian endometrioma with relief of menstrual pain, diarrhea, and other intestinal symptoms effected after only three weeks of intensive treatment. This patient was treated intermittently from May 14, 1943, to May 2, 1946, with incomplete regression of ovarian tumor, persistent, fixed, large, posterior uterus, and nodular uterosacral ligaments, but with subjective relief and no troublesome reaction.

CASE 6.—(M. T. S.), married, 28 years old, has two children; polymenorrhea with acquired left lower quadrant pain; posterior uterus, cul-de-sac endometriosis. Symptoms required 20 mg. daily orally two weeks per month intermittently for thirty months, followed by pregnancy, recently delivered.

CASE 7.—(A. D. B.), married, 35 years of age, childless; acquired menstrual pain (right labial, ischio-rectal, sciatic); cervical stenosis, right ovarian endometriosis. Testosterone (Sept. 27, 1943 to Nov. 19, 1944) relieved pain, regressed tumor, shrunk breasts slightly and uterus considerably, atrophied endometrium, reduced flow, increased libido, produced voice huskiness, no effect on normally large clitoris. Last menstrual period occurred Oct. 21, 1944 (scant under treatment[18]). Delivered July 27, 1945, less recurrent pain since.

CASE 8.—(M. H. S.), single, 25 years of age, acquired right and left lower quadrant menstrual pain, nausea, vomiting, diarrhea; appendectomy and left salpingo-oophorectomy, ruptured endometrial cyst. (January, 1943); uterus large, adnexal endometriosis. Uterus smaller, menses improved with testosterone, voice slightly hoarse.

CASE 9.—(M.E. C.), married, 27 years old, infertility, poly-hypermenorrhea with pain; right salpingo-cystoophorectomy and appendectomy for 5 cm. endometrioma, resection of left ovary; left adnexal endometriosis; regression uterus, tumor, normal flow, persistent pain (habitual) after three months' treatment.

CASE 10.—(H. P. R.), married, 34 years of age, one child, acquired menorrhagia with pain in right lower quadrant; cervicitis. Cornual myoma, and right adnexal endometriosis, cervical coagulation; methyl testosterone Oct. 17, 1944 to April 13, 1945, menses improved, adnexal tumor reduced.

CASE 11.—(F. L. M.), married, 26 years of age, two children, acquired right lower quadrant pain near menses; large uterus, uterosacral and adnexal endometriosis; with two months of intensive treatment, menses were scant, with little pain, some virilism and acne, gained weight. Examination: pelvis almost negative.

CASE 12.—(S. H. N.), married, 31 years of age, infertile, acquired abdominal and back pain, bilateral adnexal endometriosis, especially right; four months treatment, no pain with menses, right ovarian mass smaller, reaction, urticaria.

CASE 13.—(D. R. N.), single, 19 years old (courtesy Dr. Irving Uram), acquired right ureteral distribution menstrual pain, cystoscopic diagnosis; slight hydronephrosis; right simple ovarian cyst not affected by testosterone which relieved pain, therefore removed and ureteral endometrial implant diagnosed.[19-21] Testosterone discontinued, pain recurred, radical operation elected.

CASE 14.—(E. M. P.), married, 24 years of age, one abortion, acquired menstrual pain, metrorrhagia; erosion, extremely tender posterior uterus (not replaceable); large cystic right ovary, large left vaginal fornix, endometrial mass, abnormal bleeding ceased, uterus and tumors smaller under treatment.

CASE 15.—*Preoperative:* (I. L. W.), married, 51 years, three children, last eighteen years; three weeks' treatment failed to regress dense pelvic endometriosis sufficiently to permit total hysterectomy for uterine myomas. However, we believed preoperative treatment to be useful.[22]

CASE 16.—*Postoperative:* (R. D. H.), married, 34 years, infertile, menorrhagia, menstrual cramps, myomas, extensive endometriosis, including vagina, anus, rectum,[23] but *not* ovaries. Pelvic endometriosis did not regress after supravaginal hysterectomy[24] until after testosterone therapy, which has not reduced the hard vaginal infiltration appreciably, from Oct. 15, 1941 to July 22, 1946. Reaction, occasional hoarseness.

CASE 17.—(S. M. W.), married, 39 years old, one child, eleven years; acquired menstrual backache, pain right lower quadrant, prolonged menses; external tubal and cul-de-sac endometriosis; supravaginal hysterectomy, bilateral salpingo-oophorectomy. Endometriosis reactivated by estinyl, regressed with testosterone.

CASE 18.—(S. D. G.), married, 30 years, infertile; stenotic cervix, bilateral ovarian chocolate cysts, myomas, diffuse pelvic endometriosis. Operation: curettage, Rubin test, myomectomy, oophorectomy, ovarian resection. Testosterone used to inhibit disease. No pregnancy.

CASE 19.—(N. W. D.), married, 41 years, acquired menstrual pain, many vague symptoms; relaxed vaginal outlet, cervicitis, prolapse, myomas, bilateral ovarian chocolate cysts, diffuse endometriosis. Operation: repair, total internal genital extirpation. Early postoperative testosterone immediately transformed this psychoneurotic woman to normal, with extraordinarily rapid regression of low pelvic endometriosis.

We have utilized testosterone after radical operations with great advantage in two similar additional cases, and feel that it should be regularly so used.

Comment

Although androgen will help, there is obviously urgent need for endocrinologic research in a prevalent[25] and serious disease which may occur as early as 13 years of age,[26] and for which there is not yet ideal hormone control or reasonable conservative surgery.[27]

Summary and Conclusions

Clinical experience with numerous early and 19 listed advanced cases of "external" endometriosis, several of which have been treated up to four years, indicates certain usefulness of androgen therapy.

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Discussion

DR. EMIL NOVAK, Baltimore, Md.—There are some who believe that the endocrines play some part in the etiology of endometriosis, but this has never been established. All will agree, however, that endometriosis whether occurring normal within the uterine cavity or growing ectopically, as it does in pelvic endometriosis, is under the influence of the ovarian hormones. On the basis of our experience with the use of the androgenic hormone in the treatment of functional bleeding, it seems likely that this hormone does have some degree of anti-estrogenic effect upon the endometrium, presumably mediated through the pituitary, and always very temporary in its effects.

Endometriosis is not characteristically associated with excessive menstruation, but in some cases a dysfunctional factor co-exists, with functional bleeding in which testosterone may be helpful. However, I gather that Dr. Hirst advocates its use as a palliative for the dysmenorrhea so often seen with endometriosis. This is likely to be severe chiefly in those cases in which the endometriosis is fairly extensive, as with a unilateral or bilateral endometrial cyst, with or without involvement of the uterosacral area. In such cases surgery is certainly to be preferred to the continued use of testosterone, month after month and perhaps year after year. In the more moderate degrees, pain may not be severe or for that matter may be absent altogether. Moreover, such cases cannot be diagnosed before operation, although I have noted an unfortunate tendency to make a presumptive diagnosis of endometriosis simply because a patient has otherwise unexplainable dysmenorrhea.

THE SECOND STAGE OF LABOR; INTERNAL ROTATION*

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INTERNAL rotation has long been the most interesting feature of the mechanism of labor. This interest has been partly due to the fact that the etiology is unknown. A great difference of opinion has also existed with reference to the significance of failure of rotation.

This present study has two objectives. It was thought that if we could learn more exactly the time at which internal rotation occurred and study carefully the results of failure of rotation, we might possibly arrive at a more definite knowledge of why internal rotation takes place. Or, failing that, we might learn how better to manage the unrotated head.

For the past several years, we have tried to improve our labor records by noting carefully the direction of the sagittal suture and the exact presenting point with reference to the two fontanels at each successive examination during labor. Vaginal examinations have deliberately been made as frequently as necessary when exact information on these points was not available by rectal examination. During the second stage particularly, the direction of the sagittal suture was noted frequently. It was our impression that internal rotation usually takes place while the head is descending to the pelvic floor. We, therefore, made it a particularly urgent necessity to know whether this was true. As a result of having made these careful records on some 2,900 primiparas and some 2,500 multiparas, we can now say that internal rotation is complete at the time the head reaches the pelvic floor in approximately two-thirds of all patients (hereafter referred to as early rotation). In something less than 30 per cent, internal rotation is completed very shortly after the head reaches the pelvic floor. The length of time varies from as little as one uterine contraction in a multipara to as many as ten or twelve contractions in some primiparas.† In something over 4 per cent of all patients, rotation to the anterior does not take place. In a portion of these, rotation posteriorly to the hollow of the sacrum occurs. In another portion, partial rotation anteriorly is observed (as from an obliquely posterior position to an obliquely anterior position). The largest fraction of this 4 per cent, however, is made up of those patients in whom no internal rotation occurs. Two and six-tenths per cent of all primiparas and 1.4 per cent of all multiparas fall into this latter group. It should be pointed out that not all of these patients are truly "persistent" occiput anterior or "persistent" occiput posterior. Of 100 such primiparas, 25 delivered spontaneously

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	Primiparas	Multiparas
†Early	1827	1734
Late – soon –	347 – ave. 6.6 mins.	353 – ave. 3.3 mins
Late – delayed (?) –	564 – ave. 42.0 mins.	311 – ave. 17.5 mins
Late – 3 groups –	143	100

without any considerable delay and without harm to mother or baby. Thirty-two out of 42 similar multiparas delivered spontaneously with labor prolonged no more than a few minutes as a result of the unrotated position of the head. The remaining 75 primiparas and 10 multiparas were delivered by operative means. It could well be that a considerable portion of these latter groups would have rotated and delivered spontaneously had the application of forceps or manual rotation been delayed a few more minutes. (These latter four groups of patients—that is, those rotating anteriorly [either soon or a little later] after reaching the pelvic floor, those rotating posteriorly, those undergoing partial rotation, and those undergoing no rotation will hereafter be referred to collectively as "Late Rotation.")

When (and Why?)

As stated above, internal rotation occurs in approximately two-thirds of all patients by the time the head has reached the pelvic floor. In the remaining one-third, it occurs later or, perhaps, not at all. Whereas internal rotation has taken place during the first stage of labor in a very small percentage of all patients, it is, for the most part, very definitely a second-stage phenomenon. In this connection, several statements in a previous publication[1] will not be repeated here. The long-standing belief that only small round heads sometimes failed to undergo internal rotation is not borne out by this study. Not only does the same proportion of large heads (weight 3,500 Gm. and over) rotate, but the rotation occurs at approximately the same time, so that the size of infant's head or size of the infant is not a factor in this process. Similarly, failure of rotation occurs with occiput anterior as well as with occiput posterior. It is only slightly more frequent with the posterior position. Somewhat to our surprise (Table I), we found that early rotation was definitely more frequent in multiparas than in primiparas. What was even more interesting was the

TABLE I. INTERNAL ROTATION

			INCIDENCE OF LATE ROTATION (PER CENT)
Primiparas:			
Good pains	Small babies	772 Early	
		374 Late	33
	Large babies	229 Early	
		121 Late	35
Poor pains	Small babies	592 Early	
		432 Late	42
	Large babies	234 Early	
		163 Late	41
Multiparas:			
Good pains	Small babies	716 Early	
		272 Late	28
	Large babies	434 Early	
		174 Late	29
Poor pains	Small babies	349 Early	
		186 Late	35
	Large babies	235 Early	
		125 Late	35

fact that, in this series, early rotation was considerably more common with good labor pains than it was with poor labor pains.* We thus find that multiparas with good labor pains will have early rotation in 72 per cent of all cases. Primiparas with poor labor pains, on the other hand, will have early rotation in only 58 per cent of all cases. Failure of internal rotation similarly occurs in only 1.2 per cent of multiparas with good pains, and in this series was judged to have failed in 5.6 per cent of primiparas with poor pains.

Whereas the above findings do not definitely establish the etiology of internal rotation, it seems that we can very definitely state that parity and the character of the labor pains are definite factors in this process.

Significance of Late Rotation

As previously stated, the vast majority of all heads unrotated at the time the pelvic floor is reached will rotate quite promptly thereafter. In multiparas particularly, this rotation takes place during the next one or two uterine contractions. In primiparas, three to five such uterine contractions are usually necessary. In these groups of patients, this amount of delay in rotation is not evidenced in the complete pelvic floor phase of the second stage. There seems to be sufficient distention while rotation is taking place that the whole pelvic floor phase is accomplished just as quickly as though the head had been completely rotated at the time the pelvic floor was reached.

Similarly, rotation of an occiput posterior into the hollow of the sacrum and spontaneous delivery thereof, be the patient primipara or multipara, does not materially delay the completion of the delivery.

In the remaining groups, that is, those in whom internal rotation is only partly accomplished, or in whom no rotation takes place (2.6 per cent of primiparas and 1.4 per cent of multiparas), failure of rotation is a much more significant item in primiparas but not of serious import in multiparas. Even in primiparas, it is not of great importance if the labor pains are good, but if the labor pains are poor, forceps delivery was thought necessary in 75 per cent of our primiparas.

TABLE II. SECOND STAGE IN MULTIPARAS

PELVIC FLOOR PHASE		TIME (MINUTES)	NUMBER OF PATIENTS
Good pains:			
Small baby	Early rotation	8.7	716
Small baby	Early rotation	add 3.0	272
Large baby	Early rotation	9.5	434
Large baby	Early rotation	add 3.5	174
Poor pains:			
Small baby	Late rotation	12.1	349
Small baby	Late rotation	add 8.1	186
Large baby	Late rotation	14.7	235
Large baby	Late rotation	add 6.6	125

*Labor pains were said to be good for the purposes of this study if they occurred at intervals no longer than two minutes and of an intensity that would barely allow a slight indentation of the fundus of the uterus by the examiner's finger at the height of a contraction and at a point not directly over the body of the baby. They were said to be poor if of a longer interval or a lesser intensity, or both.

Table II shows these differences for multiparas in simple tabular form. The group of large baby, late rotation, and poor pains should probably be looked upon as adding something like ten or twelve minutes to the duration of the early rotation group, rather than the 6.6 minutes recorded in the table.

Table III presents the same material for primiparas. It will be observed that significant prolongation of the pelvic floor phase of the second stage is present where the labor pains are poor. It should be noted that this difference of seventeen minutes observed in late rotation for small babies is, perhaps, not far from being entirely correct. Although approximately 25 per cent of the late rotations were delivered with forceps, only a very few could be said to have prolonged second stage in this operative group. Large babies with late rotation and poor pains present a considerably different picture. In this group, the labor may be considerably prolonged. The fact that we used forceps on 40 per cent of these patients explains the apparent contradiction noted in Table III, where late rotation seemingly prolongs the second stage by only ten minutes. This figure would undoubtedly be at least thirty to forty minutes if it were not decreased by frequent operative intervention.

TABLE III. SECOND STAGE IN PRIMIPARAS

PELVIC FLOOR PHASE		TIME (MINUTES)	NUMBER OF PATIENTS
Good pains:			
Small baby	Early rotation	28.7	772
Small baby	Early rotation	add 3.7	374
Large baby	Early rotation	33.6	229
Large baby	Early rotation	add 10.8	121
Poor pains:			
Small baby	Late rotation	44.9	592
Small baby	Late rotation	add 17.0	432
Large baby	Late rotation	61.6	234
Large baby	Late rotation	add 9.9	163

Careful appraisal of Tables II and III would suggest that poor pains is a much more significant item than failure of rotation, which is apparently of equal importance to "large" baby as a deterrent to prompt completion of the second stage. Although no data are here included, we also know from recent careful observation that voluntary effort is at least equally important to the labor pains.

Table IV presents the data for these same groups of patients with incidence of operative delivery, all but very few of which were low forceps. From this

TABLE IV. FORCEPS DELIVERIES IN PER CENT

	PRIMIPARAS		MULTIPARAS
Good pains:			
Small baby	Early rotation	4.0	
Small baby	Late rotation	5.1	
Large baby	Early rotation	4.4	0.7
Large baby	Late rotation	9.1	
Poor pains:			
Small baby	Early rotation	15.5	
Small baby	Late rotation	24.3	2.2
Large baby	Early rotation	26.1	2.5
Large baby	Late rotation	39.9	6.4

tabulation, it would seem that operative delivery is rarely if ever necessary in multiparas, except perhaps in the group of large baby, late rotation, and poor pains, where approximately one out of sixteen such patients was so delivered in this series. In primiparas, we are more and more learning that forceps are not necessary where the labor pains are good, but are, perhaps, increasing our incidence of forceps deliveries in the presence of poor pains, particularly when the baby is large or rotation is late. In the complete absence of rotation, our forceps incidence was 75 per cent of that very small group of primiparas (2.6 per cent) where the pains were poor and the baby large (1.95 per cent of all primiparas). Even in this very small group, one should not proceed to the immediate application of forceps as soon as the head reaches the pelvic floor, or even in three to five pains thereafter, as a delay of thirty to sixty minutes will produce sufficient distention of the perineal tissues that the forceps delivery will be found to be much easier than if attempted immediately. Moreover, one is frequently surprised to find that rotation does occur at the end of thirty to forty minutes, when in the first fifteen or twenty minutes it had seemed most unlikely. The old rule of "not over one hour on the pelvic floor," as stated by Litzenberg, Baer, Polak, and others, is still a reliable rule.

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Discussion

DR. M. PIERCE RUCKER, Richmond, Va.—From a practical standpoint, I believe the shorter the second stage the better it is for mother and baby. If proper facilities and help are available, I see no reason why the mother should not be delivered as soon as the cervix is out of the way.

As a study in the physiology of labor, Dr. Calkins' essay is important, for when all is said and done, we cannot know too much of physiology. It is the standard by which we should measure our results. When the speaker states that in two-thirds of all patients internal rotation is complete at the time the head reaches the pelvic floor, and that in something less than 30 per cent, it is completed very shortly thereafter, we may take it that this represents the true state of affairs. In slightly over 4 per cent anterior rotation does not take place. Some of these rotate posteriorly, and in some anterior rotation is arrested, but in 3.4 per cent of all primiparas, and 1.7 per cent of all multiparas, no internal rotation occurs.

The statistical value of the paper is somewhat vitiated by the forceps deliveries. These varied from 1 per cent to 75 per cent in the various subgroups. Furthermore, the author does not state his indications for the operation. He is conscious of this possible criticism when he says that the "fact that we used forceps on 40 per cent of these patients (large babies with late rotation) explains the contradiction noted in Table III where late rotation seemingly prolongs the second stage by only ten minutes." Evidently his obstetric judgment got the better of his statistical zeal.

It is interesting to note that the size of the fetal head is unimportant from the standpoint of internal rotation or failure of rotation. The character of uterine contractions is of far greater importance. By inference the tenseness of the pelvic floor is not as important a cause of anterior rotation as we were taught to believe, for in multiparas failure of internal rotation occurs in only 1.2 per cent when the pains were good in comparison with an incidence of 2.6 per cent in primiparas. Furthermore, in two-thirds of all patients, internal rotation takes place before the presenting part hits the "pelvic trough" which we used to think was the cause of internal rotation.

I wish Dr. Calkins had discussed the role of the uterus, other than its driving power, in the failure of internal rotation. He stated internal rotation was usually a second stage phenomenon. Can it be that so long as the presenting part is within the uterus, the lower uterine segment acts as a brake on rotation?

The more we study the physiology of labor, the more we feel the need of further study of the uterus. In the past, attention to mechanical difficulties has overshadowed the importance of variations in the function of this organ. Today's paper is a case in point. The character of the labor pains is of greater importance than the size of the fetal head or the character of the perineum.

DR. CALKINS (Closing).—This paper deals with patients whose pelves (in over 90 per cent) were normal. We did not delete any abnormal pelves from the series, and it can well be that a truly abnormal pelvis will definitely affect the physiology of labor. Certainly, anything that is out of the usual may be a factor, since we as yet do not know the etiology of internal rotation itself. I cannot, therefore, answer the question as to what effect the various types of pelvis may have upon the mechanism of labor. I am trying to find out what happens when the pelvis is normal, and I still do not know. This study is only a step in that direction.

As to the question whether one may by simple finger pressure on the suture line bring about more prompt rotation, there is no question but that such can be done, particularly when rotation will otherwise be early and easy, but it cannot be so readily effected with the large head and poor pains, and that is when you really need some help.

THE OBSTETRIC MANAGEMENT OF PREGNANCY COMPLICATED BY HEART DISEASE*

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THIS paper is a review of 200 cases of pregnancy complicated by heart disease. The majority of these patients has been observed in a cardiac and obstetric clinic which was established at the Toronto General Hospital in 1933. Some patients did not receive the benefit of such observation and care, and were first seen when admitted to the hospital because of cardiac failure or the onset of labor. One hundred ninety patients had rheumatic heart disease, seven had congenital heart disease, and three had degenerative heart disease.

The cases have been divided into three groups according to the severity of their heart disease. Group I is composed of patients without impairment or very slight impairment of exercise tolerance. Group II is composed of patients with moderate to severe impairment of exercise tolerance. Group III is composed of patients with extreme impairment of exercise tolerance or cardiac failure. The number in each group is shown in Table I.

TABLE I

Group I	87 cases
Group II	80 cases
Group III	33 cases

Patients attending the cardiac-obstetric clinic are requested to report for examination every two weeks, and are seen by the cardiologist every four weeks. All patients are advised to rest a minimum of twelve hours daily, and this is increased as the pregnancy progresses or the exercise tolerance diminishes. If adequate rest cannot be obtained at home, the patient is sent into the hospital. Most patients in Group II are advised to come into the hospital for rest about one week before their expected date of confinement. Patients are warned of the seriousness of upper respiratory infection and advised to take more than usual care if such infection occurs. When possible, the normal gain in weight during pregnancy is limited by suitable diet to fifteen pounds. If the patient is obese, an effort is made to prevent any gain in weight. The development of signs of the late toxemias of pregnancy is considered serious, and immediate admission to the hospital is recommended for even mild degrees of albuminuria and hypertension. By such a regime, 170 patients have been carried to the period of viability or full term.

Thirty patients, all in Group II or III, had their pregnancies terminated before the sixth month. The indications for termination are shown in Table II.

*Read at the Fifty-Seventh Annual Meeting of the American Association of Obstetricians, Gynecologists, and Abdominal Surgeons, Hot Springs, Va., Sept. 5 to 7, 1946.

TABLE II

Failure before present pregnancy	5 cases
Failure during present pregnancy	7 cases
Marked and progressive impairment of exercise tolerance	17 cases
Acute rheumatic fever and severe myocarditis	1 case
Total	30 cases

Definite indications for the termination of pregnancy have not been established, but each case is individually assessed by considering the past cardiac and obstetric history, parity, and the present cardiac status of the patient. Twelve patients who had had cardiac failure before becoming pregnant or who developed it during the early months had pregnancies terminated after recovery from the failure or when marked improvement in their general condition had occurred. Seventeen patients had pregnancies terminated because of such marked impairment of exercise tolerance that it appeared that the added burden of late pregnancy would be greater than the heart could stand. One patient with severe myocarditis had pregnancy terminated during an acute attack of rheumatic fever. Of the 30 patients in whom pregnancy was terminated, only two were primiparous, and 20 were para two or more.

Further pregnancies are inadvisable for the majority of patients requiring therapeutic abortion because of heart disease. It is therefore advantageous to combine sterilization and therapeutic abortion if the former can be done without increased risk. This was accomplished in 22 of the 30 cases, either by hysterectomy, fundectomy, or hysterotomy with varying types of tubal resection.

TABLE III. METHOD OF TERMINATION

Dilatation and curettage	5 cases
Hysterotomy and tubal ligation	3 cases
Fundectomy	4 cases
Hysterectomy	15 cases
Bag induction	3 cases
Total	30 cases

All these cases made a satisfactory postoperative convalescence except one who, although she ultimately recovered, developed a pulmonary embolus. In eight cases the general condition of the patient was so poor that sterilization was not undertaken. In five of these the pregnancy was of three months or less duration, and termination was accomplished by dilatation and curettage. In the remaining three patients, however, the pregnancies were between four and six months, and labor was induced by rupture of the membranes and the insertion of a bag. One of these patients died from cardiac failure thirty days after termination.

Of the 170 patients who reached the period of viability, 87 were in Group I, 62 in Group II, and 21 in Group III. There was one case of twin pregnancy, one case of placenta previa, and four cases of severe pre-eclamptic toxemia. Forty patients went into premature labor. Of these, two were induced because of pre-eclamptic toxemia, and two were induced because of heart disease. These last two patients were both about seven and one-half months pregnant and appeared early in the series. At the present time they

would probably be allowed to proceed to term. Our more recent experience is similar to that of Hamilton and Thomson,[1] who found that during the last month of pregnancy there is a lessening of the cardiac strain, which is usually accompanied by clinical improvement in the condition of the patient.

Our present policy in the management of the cardiac patient during labor is to give sufficient sedative during the first stage to relieve pain and anxiety and provide adequate rest. The exhausting second stage is frequently shortened by forceps delivery under ether and oxygen or cyclopropane anesthesia. It is recognized that there is an increased danger of postpartum collapse and hemorrhage, and particular care is exercised to avoid this complication of the final stage of labor. Prior to 1933, we were of the opinion that cesarean section with sterilization was the method of choice for the delivery of the cardiac patient. Between 1928 and 1933 cesarean section was employed in 19 of 41 cases of heart disease, an incidence of 46 per cent. The method of delivery of these patients is shown in Table IV.

TABLE IV. METHOD OF DELIVERY 1928 TO 1933—41 CASES

Cesarean section	19
Forceps	6
Spontaneous	16

After a review of these cases published in 1933,[2] it was concluded that this high incidence of cesarean section was unjustified. Since that date cesarean section has not been performed because of heart disease. One hundred twenty-eight patients suffering from heart disease have been delivered, and cesarean section was employed only on three occasions, once for placenta previa, once for toxemia, and once because of previous cesarean section. The method of delivery of these 128 cases is summarized in Table V.

TABLE V. METHOD OF DELIVERY—128 CASES

Spontaneous	68
Forceps	57
Cesarean section	3

Most patients tolerated labor surprisingly well, and in no case did labor alone appear to precipitate cardiac failure. In Group II there were five patients whose labor lasted over thirty hours and in one of these, with a twin pregnancy, the duration of labor was fifty hours. Despite this, however, recovery was satisfactory in all five. In eleven cases postpartum hemorrhage developed. In five of these the hemorrhage was extremely severe and one of these patients died.

During the puerperium, all patients are advised to remain in bed for fourteen days. Patients in Groups II and III are given more prolonged bed rest according to their individual requirements.

There were eight deaths in the 200 cases, a mortality rate of 4 per cent. Four of the deaths occurred in patients who had not attended the prenatal clinic, had received inadequate or no care during pregnancy, and were first

seen by us on admission to the hospital. Two were multiparas in advanced labor with cardiac failure, one was delivered spontaneously, and the other by low forceps. Both died within twelve hours of admission to hospital. One patient, eight months pregnant, died undelivered twelve hours after admission, and the postmortem examination revealed rheumatic heart disease, bacterial endocarditis, and cardiac failure. The fourth patient was admitted in coma due to late toxemia of pregnancy. After twenty-four hours in the hospital without improvement, delivery was accomplished by cesarean section. This was recognized at the time as a desperate venture, and the patient died seventy-two hours later with pulmonary edema without regaining consciousness.

The remaining four patients who died were under our control throughout pregnancy. The first had no symptoms of heart disease and died as a result of postpartum hemorrhage. The second developed cardiac failure during the eighth month, improved slightly at term, and stood a relatively short labor and low forceps delivery very well. There was a slight improvement in the patient's condition at the end of the first week post partum, followed by a gradual relapse and death on the twenty-seventh day. The third patient went into premature labor at the eighth month during cardiac failure and had a short six-hour labor and spontaneous delivery. This patient died on the sixtieth day post partum from auricular fibrillation, multiple emboli, and cardiac failure. The fourth patient died from cardiac failure one month after termination of a four and one-half month pregnancy by bag induction.

Discussion

A mortality rate of 4 per cent for 200 cases of pregnancy complicated by heart disease emphasizes the gravity of this complication. If those patients who were not under our care for the prenatal period are excluded (21 cases), the mortality is reduced to 2.2 per cent, which corresponds closely to the mortality reported by Hamilton and Thomson,[3] who state that a 2 per cent mortality probably represents the minimum rate that can be expected in a large group of patients, even when well managed. Excluding the one patient (aged 21 years) who died from hemorrhage and was in Group I, all patients who died were more than 32 years of age, and the average age was 38.8 years. The average age of all patients reaching the period of viability was 26 years. It would appear that it is the older patient who faces the greatest risk during pregnancy. The average age of death (38.8 years) for the eight patients in this series is one year more than the average age of death of 56 consecutive female deaths due to rheumatic heart disease not associated with pregnancy taken from postmortem records of the Toronto General Hospital. This suggests that while pregnancy may be the initiating cause of cardiac failure and death in a patient with heart disease, it does not reduce the average age of death for a group of patients suffering from heart disease. Proper management during the prenatal period and the wise selection of cases for the termination of pregnancy during the early months would appear to be the prime factors in establishing a low mortality rate. The choice of vaginal delivery rather than cesarean section has not apparently unfavorably influenced the

final outcome of any case in this series. On the contrary, the avoidance of a serious abdominal operation, carrying with it an appreciable operative mortality in a "poor risk" patient, has probably contributed to a lessening of both morbidity and mortality.

The large number of cases (40) of premature labor which resulted in a fetal mortality of 17 per cent is worthy of note. Such a high fetal loss among a group of patients in whom repeated pregnancies are inadvisable is disturbing. The only apparent solution is more rest in bed during the seventh and eighth month for all patients in Group II.

The large number of pregnancies terminated (30 cases) warrants comment. Because of serious heart disease, many patient were referred for therapeutic abortion to the cardiac-obstetric clinic by their own physicians, and this undoubtedly has increased the incidence of terminated pregnancies. Patients who have had cardiac failure or who develop it during the early months of pregnancy are very unlikely to stand the added burden of late pregnancy without another cardiac breakdown. Twelve of the cases were in this category, and therapeutic abortion seemed clearly indicated. Seventeen patients had such marked impairment of exercise tolerance early in pregnancy with other clinical evidence of serious heart disease that termination was deemed advisable. There are many aspects to the problem of therapeutic abortion other than medical, and each individual problem was carefully considered and discussed with the patient herself. Every effort was made to carry to term the primiparous patient, even in the face of apparently grave risk; whereas, with the multiparous patient—the mother of two or more children—such a risk was considered unjustified. Twenty of the thirty patients in whom pregnancy was terminated had two or more living children, and only two were primiparas.

The occurrence of late toxemia in the pregnant patient with heart disease is an added serious complication and may be the initiating factor in the development of cardiac failure. It frequently occurs just at the time when the strain of pregnancy on the heart is greatest and when induction of premature labor is least desirable. Prompt hospital treatment, for even the mildest cases, and wise selection of patients for induction of labor will minimize the danger and risk to the mother.

Summary

Two hundred cases of pregnancy complicated by heart disease have been analyzed. The mortality rate for the whole group was 4 per cent, while for those patients under our control throughout pregnancy the rate was 2.2 per cent. Thirty patients had pregnancy terminated because of heart disease, and 170 patients reached the period of viability. In 40 of these the onset of labor was premature, and this resulted in a fetal mortality of 17 per cent. During recent years heart disease has not been considered an indication for cesarean section. One hundred twenty-eight consecutive cases of heart disease have been delivered and cesarean section employed on only three occasions, all for

obstetric indications. The average age of death in the whole series was 38.8 years. The average age of death of 56 consecutive female patients, proved at autopsy to have died from rheumatic heart disease not associated with pregnancy, was one year less.

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THE PROBLEM OF TALCUM GLOVE POWDER AND CONTRA-INDICATIONS FOR ITS EMPLOYMENT*

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IN SURGERY, as in every other field of endeavor, there is a constant need for resisting the temptation to take anything for granted. True progress demands the discovery and correction of old errors as well as the pursuit of new ideas. New light brought to bear upon an old situation may produce a new fact. Advantage should be taken of every opportunity to re-examine all links in the chain between cause and effect, the old as well as the new. When this is done, the backward glance will often prove to be as rewarding as the forward glance.

These observations are suggested by the results of an extension of the inquiry into the use of magnesium silicate (talcum) as a powder for gloves and other rubber articles extensively used in modern operative procedures.

Until quite recently, magnesium silicate was a substance whose role was never questioned. It played a small but seemingly benign part in the assembly of hands and materials that function in operative procedures.

The studies reviewed in this paper confirm the earlier conclusion that magnesium silicate in its application as a dusting compound for rubber gloves is a mischief-maker that should be eliminated and replaced with a safe and reliable substitute.

It has been previously demonstrated by Lambert[1] and by others[2] that magnesium silicate in the form of dusting powder acts as a foreign body irritant when it gains entrance into the body tissues. The number and the size of the crystals determine the extent of the reaction. One or more fine particles of the silicate will form lesions seen under the microscope as small fibrotic areas. When the powder has been introduced in larger quantities, large and definitely granulomatous lesions with typical foreign body giant cells will be observed.

The trouble-making crystals themselves may then be seen in these lesions between rather dense fibroblastic connective tissue bundles or in the giant cells that are produced as Nature attempts to wall off the offending substance and remove it from the body.

Unfortunately, the attempt at a purge falls short of success. The nature of magnesium silicate is such that the substance may be expected to remain within the tissues once it has found a lodging place, and it will continue to act as an irritant until it is removed.

Our previous reports have described the action of magnesium silicate in producing peritoneal adhesions after abdominal surgery, and also upon its effects

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in other areas, for instance, the nonhealing sinus tracts left along surgical incisions into the deeper tissues.

The finding of magnesium silicate crystals in scars removed by surgery inspired a subsequent study of all old healed incisional scars removed surgically after a period of several months in various hospitals. We have not been surprised to discover that in every scar so removed, definite lesions containing magnesium silicate crystals could be demonstrated.

As a result of these findings we feel free to conclude that many of our cases exhibiting postoperative incisional pain and tenderness may be charged to

Fig. 1.—Small fibrotic area around small nerves in subcutaneous tissue beneath old scar.

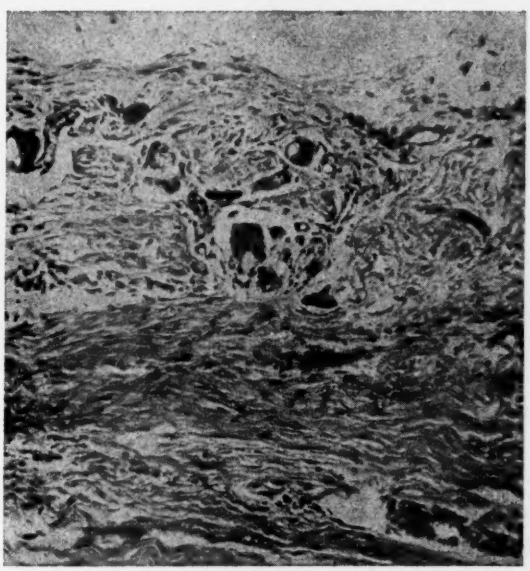

Fig. 2.—Foreign body giant cell and granulomatous reaction; subcutaneous area beneath resected recent operative scar.

inflammatory reaction generated by magnesium silicate crystals deposited by the gloved hands or drains at the time of operation.

Only a partial list of the cases studied in this series is submitted with this report, but we deem it sufficiently conclusive to merit the observation that no reason remains for not giving the situation the attention it deserves.

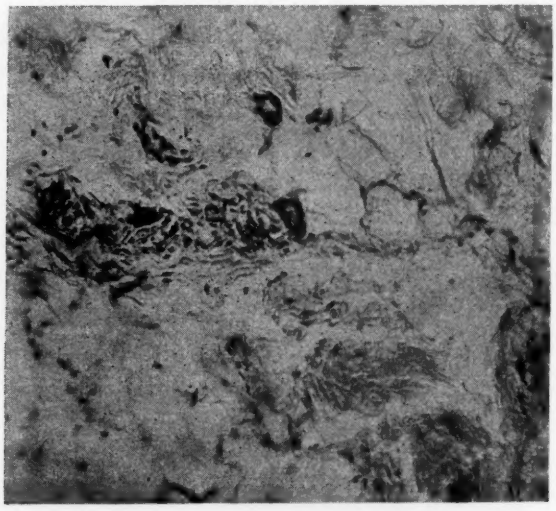

Fig. 3.—Granulomatous and fibrotic area around small subcutaneous vessels. Crystals difficult to see without polarized lighting.

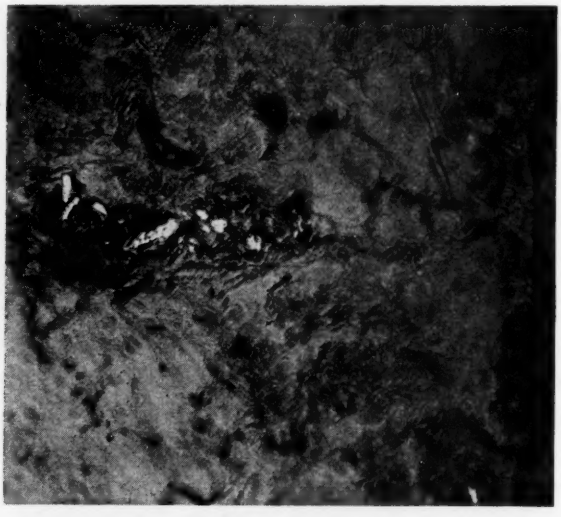

Fig. 4.—Same area as Fig. 3, as seen using polarization of light. Crystals of magnesium silicate plainly visible.

Our viewpoint simply is this — whenever the abdomen has been opened and the omentum or other tissue has been handled by the previously powdered gloved hand of the operating surgeon, careful study will demonstrate the presence of magnesium silicate crystals and a resulting reaction as described.

Beyond that point, there is no need to elaborate upon the previously reported papers covering magnesium silicate reactions. Quite plainly, it should be well recognized by this time that magnesium silicate is a harmful substance and should have no further place in the surgical procedure of our hospitals.

We may look with confidence to chemistry for an alternative substance that will serve the necessary function of a dusting compound without intruding the nonabsorbable and irritating crystalline properties of magnesium silicate. It is desirable that the substitute should be soluble in the body fluids and, at the same time, impervious to change in the sterilizing process.

Until the introduction of a substitute, practical considerations require a technique for avoiding damage for magnesium silicate. We believe that this end can be achieved by a very sparing use of cream of tarter on the hands before they are inserted into the gloves and by thorough washing of the hands after they have been gloved.

The technique we have devised for use in St. Vincent's Hospital is as follows:

1. Only enough magnesium silicate powder is applied to the inside of the gloves before dry sterilization to avoid the adhesion of their surfaces during the sterilizing process.
2. Cream of tarter is applied to the hands in small quantities, enough to assist the hands into the sterile gloves.
3. All powder remaining on the external surface of the gloves is removed by washing through two basins of sterile water.
4. All other rubber articles required in the operation are sterilized by boiling, and no powder applied.

This procedure appears to remove all but the smallest particles of the magnesium silicate powder. We submit that its observance pending the development of a substitute powder will produce a proportionate reduction in the number of postoperative lesions.

We submit several microphotograph findings in excised old and recent scars studied since 1943 at our institution, taken from the last one hundred cases.

The use of Polaroid in two planes of the microscopic light source in the manner suggested for our polarizing microscopes will aid materially in finding magnesium silicate crystals in the tissues.

Accessory parts for this purpose, cap polarizers and disc polarizers, are available and can be used with any of our modern microscopes. Properly rotated, they polarize the light in such a manner that any refractile substance in the path of the rays will be brought into clear vision. Without polarized light, many small crystals will remain invisible. Large crystals in giant cells may be observed with ordinary illumination, but in many cases cannot be studied in satisfactory detail without polarized light.

Summary

We have again called attention to the harmful effects of magnesium silicate when introduced into the body tissues in the form of surgical glove powder.

We have presented a study of resected postoperative incisional scars and omental fat showing chronic granulomatous lesions with foreign body reaction and crystals of magnesium silicate in practically every case.

We urge the adoption of a technique to minimize the hazards of magnesium silicate in surgery.

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Original Communications

A DISCUSSION OF CLASSIFICATION OF TOXEMIAS OF PREGNANCY

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THE importance of proper diagnosis and classification of disease processes is acknowledged. Often the deterrent to any advances in therapy and prognosis of a particular disease is lack of understanding of the basic pathology involved. In the human being, the underlying pathology is reflected in subjective and objective symptomatology. Any classification based, all or in part, on subjective symptoms must of necessity be fallacious, inasmuch as the personal factor in expressing subjective symptoms, both as to presence and degree, is not reliable enough to be scientifically accurate.

In order to accomplish a proper evaluation of the various toxemias of pregnancy for the purpose of setting up an adequate therapeutic regime and offering accurate prognosis, it is very important to base the classification of the particular toxemia on unequivocal objective evidence.

There have been many classifications of the so-called "toxemias of pregnancy." The various authors have found that, despite their efforts to make their classifications complete and thorough, some shortcomings could usually be demonstrated. This discussion is for the purpose of illustrating how we may better use an existing classification. An attempt will be made to show that on the basis of objective information the various toxemias can be fairly accurately differentiated. A suggestion for modification of the present classification of toxemias will be offered.

The "Classification of the Toxemias of Pregnancy" as outlined by the American Committee on Maternal Welfare and published in 1940[1] has been used as the basis for this discussion. The classification as set up by this committee is as follows:

Group A: Diseases not peculiar to pregnancy
- I Hypertensive Disease (hypertensive cardiovascular disease)
  - (a) benign (essential)
  - (b) malignant
- II Renal Disease
  - (a) chronic vascular nephritis (nephrosclerosis)
  - (b) glomerulonephritis
  - (c) nephrosis
  - (d) other forms of severe renal disease

NOTE: The Editors accept no responsibility for the views and statements of authors as published in their "Original Communications."

TABLE I. SYMPTOMS AND SIGNS

	SYMPTOMS					CARDIOVASCULAR CHANGES			
						BLOOD PRESSURE			
	ONSET IN GESTATION	HEADACHE	SCOTOMAS AND DIPLOPIA	EPIGASTRIC PAIN	EDEMA	SYSTOLIC	DIASTOLIC	HEART	PERIPHERAL VESSELS
Mild Hypertensive Disease, Hypertensive Cardiovascular Disease	before 24 weeks	slight or absent	absent	absent	slight or absent	under: 160 (often improves with rest)	100	normal or slightly larger	normal or slight change
Severe	before 24 weeks	present, often severe	usually present	absent	usually present	over: 160 (persistent after rest)	100	enlarged	hypertensive retinitis
Mild Pre-eclampsia	after 24 weeks	slight or absent	absent	absent	slight or absent	140-160 (often not persistent)	90-100	normal	normal
Severe Pre-eclampsia	after 24 weeks (may be earlier with mole)	present usually severe	present usually severe	often present (late)	moderate to severe	over: 160 (usually persistent)	100	may be enlarged	hypertensive retinitis may be present
Nephrosclerosis; Chronic Vascular Disease	before 24 weeks	present mild	present mild	absent	absent	over: 140 (persistent, may be mild)	90	normal	albuminuric retinitis
Acute Glomerulonephritis	often history of acute onset	absent	absent	absent	slight or absent	elevated	elevated	normal	normal
	(all findings may be transient and present only in the acute phase)								
Chronic Glomerulonephritis	prior to gestation	absent	absent	absent	slight	elevated	elevated	normal	retinitis
Nephrosis	prior to gestation	absent	absent	absent	present, marked	slight, if any increase		normal	retinitis may occur

Group B: Diseases dependent on or peculiar to pregnancy

I Pre-eclampsia
- (a) mild
- (b) severe

II Eclampsia
- (a) convulsive
- (b) nonconvulsive (i.e., coma with necropsy findings typical for eclampsia)

Group C: Vomiting of pregnancy

Group D: Unclassified toxemia

The symptoms and signs commonly associated with the diseases listed in the classification have been tabulated (Table I) for comparison and study.

The diseases not peculiar to pregnancy are considered pseudotoxemias and are included in the classification because "the underlying pathologic lesion or lesions of each of these diseases tend to be aggravated by the increased physiologic demands of the pregnant state and tend to produce symptoms one or more of which simulate those of preeclamptic toxemia and/or of eclampsia, or of both."[1] Differentiation of the "true" from the "false" toxemias is often difficult, and requires careful study and evaluation.

OF TOXEMIAS OF PREGNANCY

RENAL FUNCTION	ALBUMINURIA	SPECIFIC GRAVITY URINE	MICROSCOPIC URINE	BLOOD CHEMISTRY				RESPONSE TO TREATMENT
				URIC ACID	NON-PROTEIN NITROGEN	RATIO URIC ACID /N.P.N.	CO_2 COMBINING POWER	
normal	trace only	normal	negative	normal	-------	------- (may be up)	-------	Good
often impaired	trace usually	may be lowered	negative	normal	-------	------- (may be up)	-------	Fair to poor
normal	under 6 Gm./L. (2+)	normal	negative	may be high	normal	often up	normal	Usually good
normal or slightly impaired	over 6 Gm./L. (3, 4+)	normal	casts and red cells may occur	usually high	normal	usually up	often decreased	Blood pressure often increases despite diminishing edema
impaired	present	under 1.020 (urea clearance low)	usually negative	increased if severe	-------	may be up	may be low	Poor
may be impaired	present	normal high or low	casts and red cells	may be normal or increased				Usually good
progressive failure	present	usually low	casts and red cells	increased	-------	normal	often low	Fair to poor
often normal	marked	often high	no casts or cells	normal (in serum: low protein high cholesterol)	-------	-------	-------	Poor

Comparing mild hypertensive disease with mild pre-eclampsia (Tables I and II) one notes that all the findings are fairly common, except the time of onset of the symptoms. Hypertensive disease may manifest itself before twenty-four weeks gestation, pre-eclampsia usually after twenty-four weeks. However, in any of the diseases "not peculiar to pregnancy" the appearance of symptomatology may be after twenty-four weeks, not because the disease is due to the pregnancy, but because the pregnancy may have served to light up already existing pathology. Therefore, the differentiation of these two is difficult and often impossible during the pregnancy. Following the termination of the pregnancy, the persistence of any or all the signs for more than 12 to 16 weeks, or a similar designated arbitrary period, will make it probable that the disease is not peculiar to pregnancy, and therefore hypertensive rather than pre-eclamp-

TABLE II. DIFFERENTIATION OF HYPERTENSIVE DISEASE FROM PRE-ECLAMPSIA

HYPERTENSIVE DISEASE	PRE-ECLAMPSIA
1. Onset before 24 weeks gestation	1. Onset after 24 weeks gestation
2. Persistence after pregnancy	2. Disappearance after pregnancy

tic. However, hypertension may persist following pre-eclampsia, confusing differentiation, often for many months.[2]

Comparison of severe hypertensive disease with severe pre-eclampsia will elicit a like set of facts and differentiation is sometimes difficult, especially if the first sign of disurbance occurs after 24 weeks gestation. The more pronounced edema, proteinuria, and frequent oliguria in severe pre-eclampsia often serve to differentiate the two. The hypertensive with considerable proteinuria, not cardiac in origin, is usually in some degree of renal failure and has a diminished urea clearance. The urea clearance usually remains normal in the pre-eclamptic.[3] Absolute differentiation can be made only if: (1) hypertension occurs early in the first trimester (in hypertensive disease); or (2) the whole pattern disappears early in the puerperium (pre-eclampsia) (Table II).

Nephrosclerosis or chronic vascular disease occurs in the first 24 weeks of pregnancy and, more often, long before that time. Although some of the findings are common with those found in hypertensive disease (before the nephrosclerotic phase) or in pre-eclampsia, there are several items that are characteristic enough to be differential (Table III). Albuminuric retinitis is severe in nephrosclerosis and more marked than seen in the other conditions, although hypertensive retinitis may occur in the severe hypertensive or pre-eclamptic. In nephrosclerosis, urinary specific gravity is always below 1.020, and often remains low and fixed and the urea clearance is low. In severe hypertensive disease, the specific gravity of the urine as well as the urea clearance is lowered. Of course, one must be mindful that in the late stages of severe hypertensive disease we actually are dealing with a "chronic vascular disease" so that differentiation from nephrosclerosis may be impossible. In severe pre-eclampsia, urinary specific gravity and urea clearance are normal. Persistence after puerperium differentiates nephrosclerosis from pre-eclampsia.

TABLE III. DIFFERENTIATION OF NEPHROSCLEROSIS, HYPERTENSIVE DISEASE, AND PRE-ECLAMPSIA

	NEPHROSCLEROSIS	HYPERTENSIVE DISEASE	PRE-ECLAMPSIA
Occurrence	Before 24 weeks gestation, usually	Any time, before 24 weeks gestation usually	After 24 weeks gestation
Persistence	After pregnancy	After pregnancy	Disappears after pregnancy
Retinitis	Albuminuric, marked	Hypertensive, may occur if severe	Hypertensive, may occur if severe
Urine specific gravity	Always less than 1.020, often fixed	May be lowered, if severe	Normal
Urea clearance	Low	May be lowered	Normal

Glomerulonephritis with its history of acute onset, often febrile, is characteristically differentiated from the other renal diseases by the transient hypertension and the urinary findings of red blood cells and casts. The acute phase is rare in pregnancy. The chronic phase resembles mild pre-eclampsia, but urinary casts and red blood cells along with diminished renal function are differential.

Nephrosis is characterized by a marked edema with little, if any, elevation in blood pressure. Study of the blood serum reveals low protein and high

cholesterol. The disease may occur early and persist entirely unrelated to the pregnancy.

The aggravation of existing hypertension, proteinuria, and edema in the diseases "not peculiar to pregnancy" occurring after twenty-four weeks gestation must be construed to indicate the presence of superimposed pre-eclampsia.[2] Thus, a "true toxemia" is grafted onto the existing "pseudotoxemia." The return of values to prepregnancy levels during the puerperium or shortly thereafter corroborates such a diagnosis. Thus, the patient with uncomplicated essential hypertension whose blood pressure rises significantly (more than 20 mm.) and who also develops proteinuria and edema can be considered to have pre-eclampsia superimposed upon the essential hypertension, especially if in, or after, the puerperium the edema and proteinuria disappear and leave only the hypertension, at prepregnancy level.

Apart from the differentiation of those diseases peculiar to pregnancy from those independent of it, the classification also differentiates mild from severe pre-eclampsia. One may often be misled by the subjective complaints of the patient into considering her condition "mild" pre-eclampsia when, objectively, severe pre-eclampsia exists. Catastrophically, eclampsia may occur in patients demonstrating no objective findings other than those of mild pre-eclampsia.

TABLE IV. DIFFERENTIATION OF MILD AND SEVERE PRE-ECLAMPSIA

PRE-ECLAMPSIA	EDEMA	BLOOD PRESSURE		PROTEINURIA	RESPONSE TO THERAPY
		SYSTOLIC	DIASTOLIC		
Mild	Slight or absent	140 to 160 (often not persistent)	90 to 100	Less than 6 Gm./liter (2+)	Usually good
Severe	Moderate to severe	Over 160 (usually persistent)	Over 100	More than 6 Gm./liter (3 to 4+)	Blood pressure often increases despite diminishing edema

If only objective findings are adhered to, the criteria of mild and severe pre-eclampsia are clear cut and definite. (Table IV.) The mild pre-eclamptic patient has slight or absent edema, a blood pressure over 140/90 that may go to 160/100, but is often not persistently elevated, and a proteinuria up to 6 Gm. per liter, i.e., 2+. Put to bed under the proper regime, this patient usually improves all these findings. The severe pre-eclamptic patient has moderate to severe edema, a blood pressure over 160/100, and more proteinuria than 6 Gm. per liter, i.e., 3 to 4+. Put to bed and treated, the severe pre-eclamptic may improve somewhat, but not nearly to the degree that the mild pre-eclamptic does, and often the high blood pressure persists or increases despite diminishing edema or proteinuria.

The diagnosis of pre-eclampsia should be based on the occurrence of two of the three objective findings: hypertension of 140/90, edema, and proteinuria, preferably when the patient is not in labor, but may be made if elevation of blood pressure or proteinuria occurs on two separate observations twenty-four hours apart. It is felt justified to make a diagnosis of severe pre-eclampsia if on two separate observations, at least twenty-four hours apart, not during labor, two of the three criteria are valid, that is, blood pressure over 160/100, more proteinuria

than 6 Gm. per liter, or more than mild edema. Thus, the occurrence of one incident of findings in the "severe" category is not valid evidence for classifying a pre-eclampsia as severe.

It must be emphasized at this time that the differentiation between "mild" and "severe" pre-eclampsia is of hardly more than academic interest. Actually the differentiation should be dropped from the classification entirely. Cosgrove and Chesley, in discussing the relationship of eclampsia to the diagnosis of the toxemia prior to convulsion, state that "one cannot assume that a case of mild pre-eclampsia is in no danger of eclampsia . . . almost two-thirds of all our eclampsia occurred in cases which we had considered mild pre-eclampsia . . . one out of every 29 of our mild pre-eclamptics became abruptly eclamptic without any intermediate phase which would warrant their consideration as severe pre-eclamptics."[4]

It is worthy of note, and regrettable, that the classification fails to make use of the blood chemistry findings in pre-eclampsia as an objective yardstick for the prognostic evaluation of the toxemia.

Standar and Cadden conclude that "frequently repeated blood chemistry studies in 108 eclamptic and 40 pre-eclamptic patients . . . show that the blood chemistry is an indispensable index of the severity of the disease and of the specific treatment needed."[5] Our experience has shown that the clinically so-called "mild" pre-eclampsia may, by virtue of the deterioration of blood chemistry values, serve notice of the actual severity of the biochemical disturbance, and therefore warrant considerably more concern than the triad blood pressure, proteinuria, and edema might suggest.

Chesley has pointed out that a uric acid/nonprotein nitrogen ratio exceeding 10 per cent is indicative of renal impairment.[6] In reviewing a random five-year period (1935-1939) at the Margaret Hague Maternity Hospital, it was noted by the author that there were 90 cases of eclampsia, of which 35 were in the hospital before the first convulsion. Of these 35, 23 (65.6 per cent) were classified as "mild pre-eclampsia" before the first convulsion.

Thirteen eclamptics of this group, definitely classifiable as mild pre-eclamptics prior to convulsion, had blood chemistries taken before the first convulsion (Table V). All thirteen of these patients had a uric acid/nonprotein nitrogen

TABLE V. BLOOD CHEMISTRY VALUES IN ECLAMPTIC PATIENTS PRIOR TO CONVULSION

PATIENT	DAY OF BLOOD CHEMISTRY BEFORE CONVULSION	URIC ACID MG./%	NONPROTEIN NITROGEN MG./%	URIC ACID/N.P.N. RATIO (%)
1	3	4.4	30.3	14.6
2	Day of	5.6	38.0	14.8
3	Day of	6.0	45.0	13.4
4	Day of	6.4	48.0	13.4
5	4	4.4	34.0	13.0
6	Day of	6.8	29.4	23.1
7	6	5.4	33.0	19.4
8	Day of	5.6	34.0	16.5
9	13	4.6	36.0	12.8
10	Day of	5.0	34.0	14.7
11	8	5.0	27.0	18.5
12	Day of	6.7	32.0	21.0
13	1	6.0	48.0	12.5

ratio exceeding 10 per cent (12.5 to 23.1 per cent). In a summary of the blood chemistry findings in the 108 eclamptic patients studied by Stander and Cadden, the average uric acid/nonprotein nitrogen ratio was 12.6 per cent before convulsion, and 16.9 per cent during convulsion. Moreover, in reviewing the blood chemistry findings in 20 consecutive eclamptics in the same series of 108 eclamptic patients, it was found that all 20 had uric acid/nonprotein nitrogen ratios exceeding 10 per cent (13.7-21.6 per cent) in blood chemistries taken during the convulsion.[5] These statistics point up the necessity of including blood chemistry values in the criteria for the classification of toxemias of pregnancy.

Therefore, the diagnostic criteria of toxemia of pregnancy should be: (1) blood pressure, (2) proteinuria, (3) edema, (4) blood chemistry. If the diagnosis of pre-eclampsia is valid, by the present standards, it should be classified and considered severe if the uric acid/nonprotein nitrogen ratio exceeds 10 per cent.

Eclampsia of the convulsive type is self-explanatory. The findings of pre-eclampsia to which is added a convulsive seizure constitutes eclampsia. The nonconvulsive type is a diagnosis based on postmortem finding of eclamptic pathology following coma and death in a pregnant woman. Nonconvulsive eclampsia is not a clinical diagnosis.

Vomiting of pregnancy, as suggested by the American Committee on Maternal Welfare, may or may not be a toxemia. The occurrence in pregnancy of persistent vomiting is, per se, a diagnosis. Whether the vomiting is "due to the pregnancy" or just incidental to it is moot and not to be considered here.

The so-called "unclassified toxemias" are those cases which cannot be placed in the proper category during the pregnancy. During the puerperium and with follow-up study or necropsy, these cases will be found to fit into one of the other groups, A or B.

The accurate and proper appraisal of the objective signs in patients is of great value because the exact diagnosis and classification makes it possible to set up the necessary and correct therapeutic regime during the pregnancy and afterward. It makes a more intelligent prognosis available as to future life and as to the possible course of future pregnancies. Proper classification makes available accurate statistics, which are of utmost importance to the acuity and advance of any branch of science.

Summary

1. The classification of the toxemias of pregnancy of the American Committee on Maternal Welfare has been presented and analyzed.

2. Certain objective findings which may serve as points of differential diagnosis of the various toxemias of pregnancy have been pointed out.

3. The necessity for blood chemistry studies and evaluation has been demonstrated, and the inclusion of blood chemistry as a criterion of classification has been suggested.

4. Abandonment of the designations "mild" and "severe" in the classification of pre-eclampsia has been suggested.

5. The importance of proper diagnosis and classification of toxemias of pregnancy has been stressed; the value of accurate classification for therapy, prognosis, and statistical study has been emphasized.

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A PRELIMINARY EVALUATION OF DIENESTROL IN THE MENOPAUSE

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THE synthesis of stilbestrol by Dodds and his co-workers[1] and the later development of other synthetic estrogenic compounds have caused a widespread interest in the clinical value of these substances. Over a hundred synthetic compounds have been shown to be estrogenic in varying degrees. A large number of investigators have reported on the value of such synthetic compounds, compared with natural estrogens, in the control of menopausal symptoms, in the treatment of senile vaginitis and juvenile vulvovaginitis, and in the suppression of lactation. It has been clearly demonstrated that certain synthetic estrogens are not only as effective as the natural estrogens, but are as therapeutically potent when administered orally as the natural estrogens are when given parenterally.[2-6]

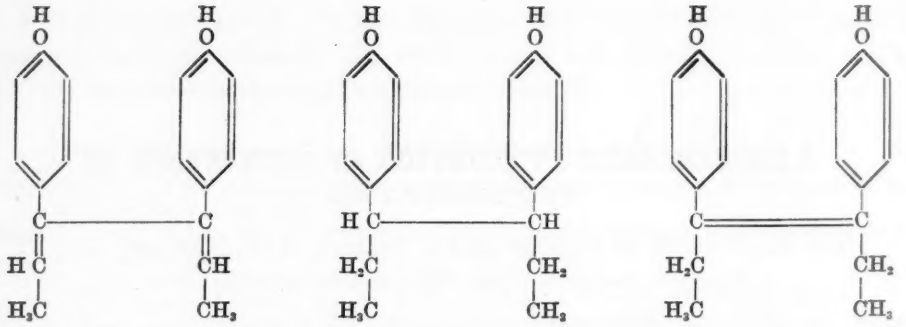
The most desirable estrogen, from a clinical viewpoint, is one that is nontoxic in addition to possessing a potent estrogenic activity that is prolonged in effect. Clinical investigation has shown that the use of the better known synthetic estrogenic compounds is accompanied, more or less, by undesirable side-reactions. Gastrointestinal symptoms are the most frequent untoward reactions noted. Their incidence has been reported to occur in from 6 per cent to 87 per cent of cases treated with various estrogenic substances.[5-9]

History of Dienestrol

In searching for the ideal estrogen, we undertook to study the clinical effectiveness of the "hexadiene compound" of Dodds, more recently designated dienestrol by the British General Medical Council.

The chemical and physical properties of dienestrol were first reported in 1938 by Dodds and his co-workers.[10, 11] The chemical configuration of dienestrol (*A*) reveals that it differs from hexestrol (*B*) and stilbestrol (*C*) with respect to the number of double bonds (degree of unsaturation) in the molecules. The two double bonds in the substituent side-chains are believed to contribute to the greater biological activity of dienestrol (see graph).

Because of its difficult synthesis, dienestrol has not been made available to clinicians until relatively recently. Emmens,[12] in 1939, showed that when dienestrol was orally administered to mice it had the greatest activity, compared with subcutaneous administration of any of the estrogens examined up to that time. Barnes[4, 13] found this compound, administered orally to human subjects, to be a potent, safe, and nontoxic estrogenic substance. She achieved therapeutic response, in suppression of lactation, with dienestrol in one-tenth the dose required in the case of stilbestrol and hexestrol.



A B C

Present Study

This study concerns our experiences in treating a total of 80 clinic and private menopausal patients with orally administered dienestrol.* Daily doses of the drug ranged from 0.2 mg. to 1.5 mg. according to the severity of the symptoms. Since seven patients were uncooperative (failing to return to the clinic or to adhere to prescribed dosage of medication), our statistics are based on our observations of the therapeutic efficacy of dienestrol in 73 menopausal patients.

The average age of our patients was 48.5 years; the youngest was 32 and the oldest 65 years of age. Thirty-six, or approximately 50 per cent, of these patients had received estrogenic therapy in some form previous to this study.

Our patients complained of the usual symptoms associated with the female climacteric. The causes of these symptoms are tabulated in Table I, and their incidence in this group of patients is listed in Table II. Clinical observations were continued for periods of two to six months.

The efficacy of dienestrol therapy was determined by the effect of the drug on the climacteric symptoms and by vaginal smear examination after the

TABLE I. CAUSES OF CLIMACTERIC SYMPTOMS

Spontaneous menopause	43	(58.9%)
Hysterectomy	16	(21.9%)
Castration	2	(2.7%)
Radiation	5	(6.8%)
Premature ovarian failure	7	(9.5%)
Total	73	(100.0%)

TABLE II. INCIDENCE OF SYMPTOMS

Flushes	63	(87.6%)
Chills and sweats	34	(46.5%)
Irritability	36	(49.3%)
Nervousness	55	(75.3%)
Vertigo	39	(53.4%)
Lack of mental concentration	30	(41.09%)
Mental depression	28	(38.3%)
Sleep disturbances	51	(69.8%)
Headaches	48	(65.7%)
Gastrointestinal disturbances	15	(20.5%)
Generalized vague aches	43	(58.9%)

*Dienestrol tablets (0.1 mg. and 0.5 mg.) were supplied by White Laboratories, Inc., Newark, N. J.

TABLE III. RESULTS OF VAGINAL SMEAR EXAMINATIONS

	BEFORE DIENESTROL	AFTER DIENESTROL
Low estrous	23	9
Estrous	22	56
Nonestrous	26	6
Not done	2	2
Total	73	73

method of Papanicolaou and Shorr.[14] Vaginal smear examination was not done in two cases for personal reasons of the patients. Results of vaginal smears are shown in Table III.

Results of Study

Three (4.1 per cent) of our patients were suffering from other medical complications, such as mental depression, alopecia areata following hysterectomy, and psychoneurosis, and presented no clear-cut indications for estrogenic therapy. No appreciable effect of estrogenic replacement therapy was noted in these patients.

Prompt relief of symptoms was reported by the remaining 70 patients (95.9 per cent). Those who had received previous estrogenic therapy reported that their symptoms were quickly and fully relieved by dienestrol, even though some of these patients had not had complete alleviation of their symptoms by estrogenic preparations previously used. Dienestrol also seemed to effect a sense of well-being, to allay apprehension, and to give patients renewed energy.

Improvement in vaginal smears generally corresponded with the clinical improvement reported. In a few cases clinical improvement was obtained without any marked change in the vaginal smear. In certain other cases, particularly those suffering with various neuroses, there was an improvement in the vaginal smear, although no clinical improvement was reported by these patients, denoting that appropriate dosage of dienestrol had been administered.

Untoward Effects.—Of this group of patients, only five (6.8 per cent) complained of pelvic congestion when dienestrol was continued over a long period of time. Two (2.7 per cent) instances of withdrawal bleeding were noted, but in each of these cases the bleeding was very mild and of short duration.

Three of our patients complained of slight nausea during dienestrol therapy. One of these was under concurrent treatment for gall bladder disease, while another stated that she reacts unfavorably to any new medication. Excluding the latter two cases, the incidence of nausea in our series of 73 patients, therefore, was limited to one case (1.3 per cent). This low incidence of nausea is, in our experience and the experience of other investigators,[5-9] in contrast with that encountered during treatment with other synthetic estrogens.

Case Reports

CASE 1.—*Premature ovarian failure:* Mrs. M. H., aged 47 years; married, no children. *Complaints:* hot flushes (20 per day); chills, occasional headaches, especially on first day of period; nervousness; irritability; vertigo; paresthesia of hands; and arthralgia. *Past history:* no serious illnesses; no surgery. *Examination:* Blood pressure, 130/90; pulse, 76; weight, 196½ pounds; heart, negative; no evidence of pelvic pathology. *Vaginal smears:* 5/5/46—2 plus (nonestrous phase); 5/10/46—4 plus (full estrous phase); 5/24/46—4 plus. *Therapy:* One milligram of dienestrol daily initiated 5/5/46. *Results:* Improvement in all symptoms. Slight paresthesia persists.

CASE 2.—*Spontaneous menopause:* Miss G. Y., aged 49 years, single. *Complaints:* few hot flushes; pressure on top of head; mild insomia; vertigo; heaviness of eyes; dryness of skin; alopecia areata; stiffness of legs; paresthesia. *Past history:* no surgery. Previous estrogenic therapy caused aggravation of flushes and uterine bleeding became profuse and clotted. *Examination:* Blood

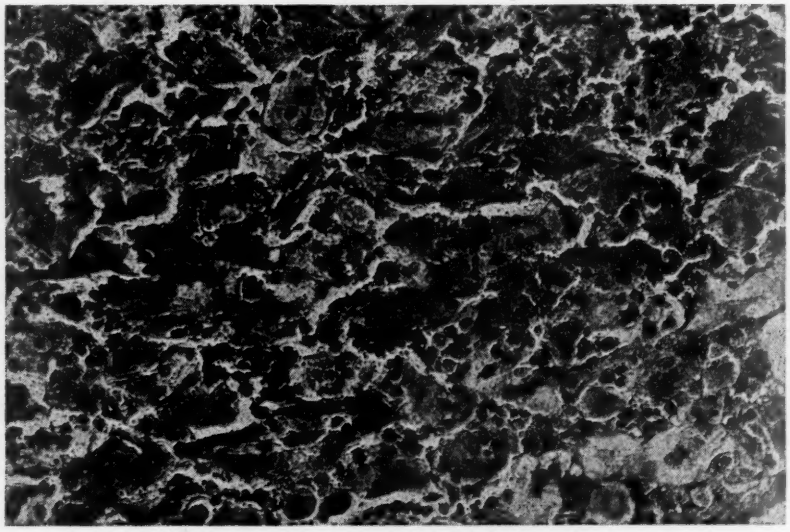


Fig. 1.—Miss G. Y., aged 49 years, 4/29/46. Before therapy—nonestrous phase.

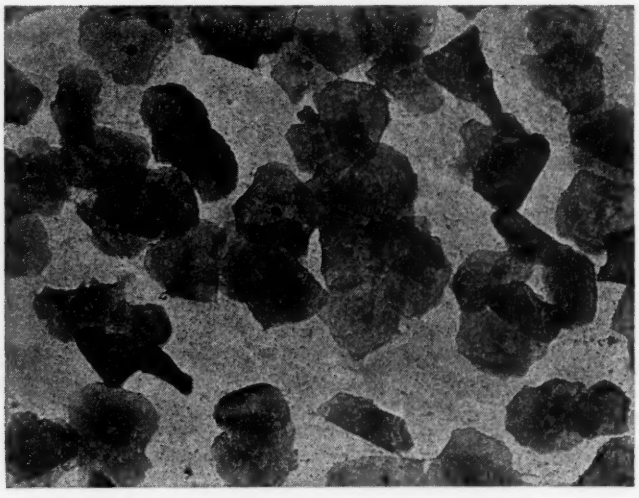


Fig. 2.—Miss G. Y., aged 49 years, 5/18/46. After three weeks' therapy—hyperestrinization.

pressure, 110/60; pulse, 76; basal metabolism rate, plus 5 per cent; weight, 151 pounds. Senile regression of pelvic organs and mucous membranes. *Vaginal smears:* 4/29/46—1-2 plus (nonestrous phase); 5/5/46—2 plus; 5/18/46—5 plus (hyperestrinization phase). (See Figs. 1 and 2.) *Therapy:* One milligram dienestrol daily starting 4/29/46. *Results:* Excellent improvement in all symptoms.

CASE 3.—*Hysterectomy one month previous:* Mrs. B. B., aged 37 years, married, three children. *Complaints:* Hot flushes; perspiration; mastalgia;

migraine headaches of three years' duration; mental depression. *Past history:* Ovarian resection and suspension in 1940 followed by hot flushes which gradually became worse. Hysterectomy one month previous to this study. Moderate improvement of symptoms on premarin therapy. *Examination:* Blood pressure, 104/60; pulse, 64; weight, 131½ pounds. Pelvis negative. *Vaginal smears:* 12/11/45—1 plus; 1/5/46—2 plus; 2/1/46—2 plus; 2/14/46—2 plus;

Fig. 3.—Mrs. P. H., aged 54 years, 5/8/46. Before therapy—nonestrous phase.

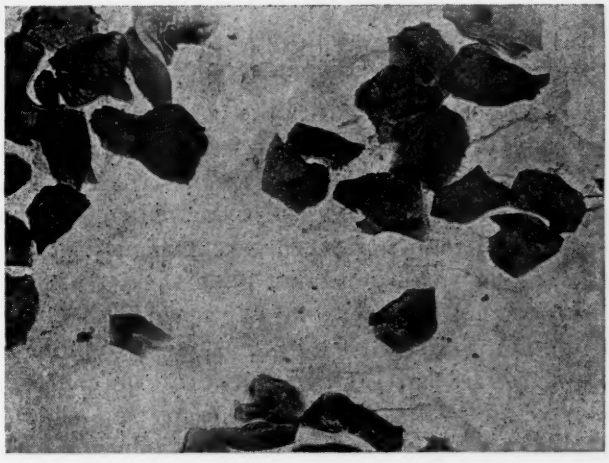


Fig. 4.—5/28/46. After 20 days' therapy—full estrous phase.

2/19/46—3 plus; 3/1/46—3 plus; 5/27/46—1 plus. *Therapy:* Premarin was discontinued and dienestrol started in 1 mg. daily doses on 12/11/45. *Results:* There was a gradual improvement in vaginal smears and dosage was decreased to 0.3 mg. and later to 0.2 mg. of dienestrol daily. Good results were maintained on 0.3 mg. daily. Some symptoms recurred on 0.2 mg. daily. Patient still complained of neuralgia and thiamine chloride was added on 3/1/46. Dienestrol was increased to 0.5 mg. daily and best results obtained. On decreasing dosage of medication the quality of the vaginal smears decreased.

CASE 4.—*Spontaneous menopause.* Mrs. E. Q., aged 51 years, married, two children. *Complaints:* hot flushes, worse at night; insomnia; headaches;

vertigo; generalized aches; vaginal pruritus. *Past history:* No surgery. *Examination:* Blood pressure, 120/70; pulse, 80; weight, 137¾ pounds; heart, negative; urinalysis, negative. *Pelvic:* Uterus normal in size and position; intracervical polyp: senile regression. *Vaginal smears:* 3/6/46—2 plus; 3/20/46—3 plus; 4/9/46—3 plus; 5/14/46—4 plus. *Therapy:* Dienestrol, 0.3 mg. daily, initiated 3/6/46; increased on 3/20/46 to 1 mg. daily. *Results:* Excellent improvement in all symptoms.

CASE 5.—*Spontaneous menopause of two months' duration:* Mrs. R. C., aged 49 years, married, five children. *Complaints:* Irregular periods past year; hot flushes; nervousness; insomnia and headaches; arthralgia. *Past history:* Appendectomy at 22 years of age. Irregular estrogenic therapy (premarin) —none since January, 1946. *Examination:* Blood pressure, 100/60; pulse, 70; weight, 128 pounds; heart, negative; urinalysis, negative. *Pelvic:* cystocele and rectocele. *Therapy:* Dienestrol, 0.3 mg. daily, initiated 4/16/46; gradually increased to 1.5 mg. daily. *Vaginal smears:* 4/16/46—2 plus; 4/30/46—3 plus; 5/20/46—3 plus; 6/10/46—1 plus, 6/24/46—4 plus. *Results:* Excellent improvement in all symptoms.

CASE 6.—*Hysterectomy 12 years ago:* Mrs. P. H., aged 54 years, married, two children. *Complaints:* Hot flushes every half hour (no relief from estrogenic therapy); headaches; left mastalgia; pain in left shoulder; mental depression. *Past history:* Appendectomy and hysterectomy twelve years ago. Hot flushes started three weeks after hysterectomy. *Examination:* Blood pressure 124/80; pulse 84; urinalysis negative. *Pelvic:* senile regression of pelvic organs and mucous membranes. *Therapy:* Dienestrol, 1.5 mg. daily, initiated 5/8/46, decreased on 6/20/46 to 1 mg. daily. *Vaginal smears:* 5/8/46 —nonestrous; 5/28/46—4 plus (see Figs. 3 and 4). *Results:* Improvement in all symptoms.

Comment

Approximately 50 per cent of our patients had received estrogenic therapy in some form previous to this study. This was inadequate either in dosage or in continuity of therapy, since their symptoms were not relieved thereby. Because of this, many of our patients had a vaginal smear which showed a low estrogenic phase at the time dienestrol therapy was instituted.

Daily dosage of dienestrol depended upon the severity of the symptoms. Some patients whose symptoms were not very pronounced were placed on low doses. It is our opinion that for good initial effects, to build up the confidence of the patient, and prove that the symptoms can be controlled, larger doses should be employed in the beginning of therapy but should be quickly reduced to a maintenance dose with periods of interruption of therapy. We have determined, from our series of patients, that a maintenance dose of 0.3 mg. dienestrol daily is ideal. We have noticed that interruption of therapy takes place almost automatically since the patients either forget to take the tablets or are only too glad to discontinue medication when symptomatic relief is obtained. Most of our patients state that they get very weary of swallowing pills and remember them only when symptoms recur.

A large number of our patients lowered the dosage of dienestrol of their own accord, or discontinued it entirely when they were free of symptoms and did not return for recheck until symptoms returned. A few patients claimed they could be maintained on 0.2 mg. daily or 0.5 mg. two or three times weekly.

It has been our experience that the more systematic the regime of estrogenic therapy, the better and more uniform is the response.

Conclusions

1. Orally administered dienestrol gave prompt symptomatic relief in 70 menopausal patients in whom estrogenic replacement therapy was clearly indicated. Vaginal smear response to treatment generally corresponded with symptomatic improvement.

2. The unusually low incidence of gastrointestinal intolerance (1.3 per cent) and the absence of other toxic side effects make this preparation particularly commendable.

3. Dienestrol is a potent, safe, and unusually well-tolerated synthetic estrogenic substance.

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DYSGERMINOMA OF THE OVARY

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TWO cases of dysgerminoma of the ovary are reported herewith. One is of interest because of the association of dysgerminoma with a normal pregnancy; the other because of normal menstruation associated with dysgerminoma in the presence of marked underdevelopment of the internal genital organs.

CASE 1.—A 21-year-old white woman, admitted, August, 1944, to the Oakland Regional Hospital, with the chief complaint of constipation of two and one-half months' duration, amenorrhea of two months' duration, and a symptomless mass in the abdomen first noticed on June 22, 1944, approximately two months previously.

Past history showed that menstruation began at the age of 12 years and recurred every thirty-five days. Duration was four days; amount of flow was normal. Last menstrual period occurred June 7, 1944, two months prior to admission. Early in June, 1944, the patient first began to notice constipation. This condition became steadily worse until the time of admission, when cathartics and enemas were required. The mass in the abdomen was first noticed by the patient about June 22, 1944. There was no associated pain or tenderness. Increased urinary frequency and nocturia had been noticed in the last few weeks. The patient came to the hospital because she thought her symptoms were due entirely to pregnancy. She had gained ten pounds in the month prior to admission.

Physical examination showed a well-developed, well-nourished young adult white woman who did not appear ill. Secondary sex characteristics were entirely normal. The abdomen showed a midline mass which appeared to arise from the pelvis. It measured 22 cm. above the symphysis pubis. The mass was smooth, freely movable, and gave the impression of being cystic. It was not tender.

Pelvic examination showed the cervix was soft and of a congested, slightly purplish color. The body of the uterus could not be definitely outlined. A large mass was palpated in the cul-de-sac of the pelvis. Remainder of the examination was normal. Admission diagnosis was that of a large ovarian cyst.

X-ray studies of the abdomen revealed a large, soft tissue mass arising from the right side of the pelvis and extending up to L-3 (Fig. 1). Intravenous urogram showed dilatation of the right calyces, kidney, pelvis, and proximal ureter with displacement of the right ureter to the left (Fig. 2). The left side was normal. Barium enema showed a slight pressure deformity of the proximal rectum, with lateral and upward displacement of the ascending colon and cecum. The mass did not appear to be attached to the bowel. Small bowel study and chest plate were normal.

Laboratory studies showed the following: red blood cells, 3,490,000; white blood cells, 6,500; hemoglobin, 71 per cent. Urinalysis—negative; Kahn—negative; Friedman test—positive on two occasions.

Repeated pelvic examination showed the coexistence of two separate masses, one of which was then assumed to be a large ovarian cyst, and the other a normal pregnancy of about three months' duration. Exploratory laparotomy was performed through a lower right rectus muscle splitting incision. The uterus was found to be enlarged to the size of a three and one-half month pregnancy. A large, freely movable nodular mass was found lying on the right side of the abdomen and attached to the right broad ligament by a definite pedicle. The

tumor seemed to be a solid ovarian tumor. It was removed intact after ligating the pedicle. Further abdominal exploration was unrevealing, the left ovary and tube being normal in appearance.

Postoperative convalescence was uneventful. The patient was discharged on the thirteenth postoperative day. Radiation therapy was deemed inadvisable.

Pathologic Description.—Specimen consisted of an ovarian mass which was entirely encapsulated and measured 19 by 13 by 11 cm. It was attached to a small pedicle which measured approximately 2 cm. in diameter. The general contour of the mass was somewhat kidney-shaped and slightly nodular. On section, it cut with ease. However, the mass seemed to be composed of solid tissue

Fig. 1.

which was gelatinous, edematous, and brainlike in consistency. There were small scattered cystic areas up to 1 cm. in diameter throughout the entire tumor, and in some areas there was hemorrhagic extravasation into the tissues. Microscopically (Fig. 3), this tissue was composed of nests, masses, and cords of large cells which had a granular and vesicular nucleus and a clear cytoplasm with a well-defined cell margin. The cells varied somewhat in size. There were numerous typical and atypical mitotic figures present. Tumor giant cells were seen throughout the sections. There was a delicate framework of fibrous tissue coursing throughout the sections, and this fibrous tissue was moderately infiltrated with lymphocytes. There was also infiltration of lymphocytes between the groups of malignant cells. Some sections showed large areas of necrosis. *Diagnosis:* Dysgerminoma of the ovary. The patient moved to another section of the country and was not contacted for some time. She was delivered of an 8 pound, 6 ounce baby girl without complication on March 8, 1945. Ex-

Fig. 2.

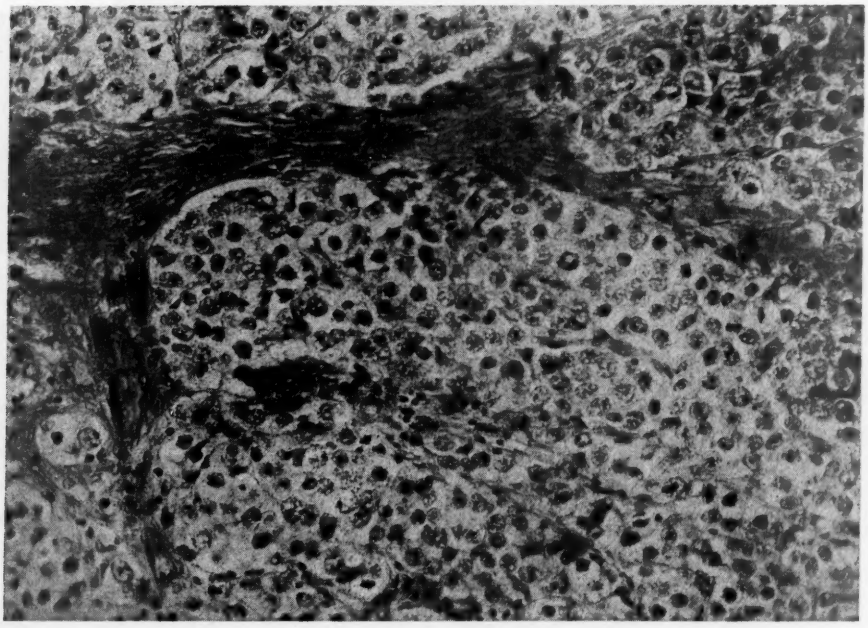

Fig. 3.—Photomicrograph shows nests and cords of carcinoma cells separated by strands of fibrous tissue. Numerous typical and atypical mitotic figures can be seen and a moderate lymphocytic infiltration is present in the fibrous tissue septa. An occasional tumor giant cell is seen throughout the section.

amination of the patient April 12, 1946, revealed that her physical condition is entirely normal in all respects. There is no evidence of recurrence or metastasis of the tumor approximately two years after its removal.

CASE 2.—A 22-year-old white woman, a WAC, was admitted Nov. 27, 1944, with a chief complaint of soreness and tenderness in the right lower quadrant, abdominal mass in that area, and moderate constipation.

Past history was as follows: Menses began at 14 years of age; regular every twenty-eight days; normal in amount; two to three days' duration. Last menstrual period had occurred thirty-one days prior to admission. No recent weight loss was noted.

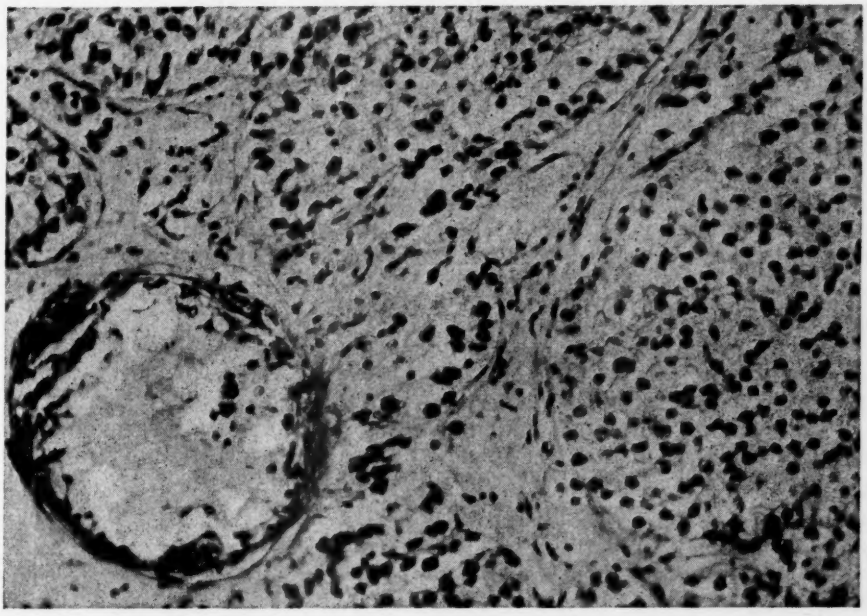

Fig. 4.—Photomicrograph shows large carcinoma cells arranged in nests and cords with a sparse and delicate fibrous tissue stroma separating the nests of cells. Moderate lymphocytic infiltration can be seen in this connective tissue. The lower margin of the section shows a small blood vessel which is apparently lined by some large carcinoma cells and has a few malignant cells in the lumen.

About two weeks prior to admission, the patient bumped the abdomen against the framework of a truck. The injured area remained sore for several days. Three days following the injury she noticed a mass in the lower abdomen which was tender on pressure. For four days prior to admission she had had no bowel evacuation.

Physical examination revealed a young white woman who did not appear ill. The body build was definitely masculine, with poorly developed breasts and a narrow pelvis. Hirsutism was of normal feminine type. There was a mass in the lower abdomen which seemed to arise from the right side of the pelvis. It filled the right lower portion of the abdomen to the level of the umbilicus and gave the impression of being cystic to palpation. Pelvic examination was unsatisfactory because of an intact hymen. Rectal examination showed the true pelvis to be empty. No uterus or cervix could be palpated. The external genitals were of normal female type. Remainder of the examination was entirely negative.

Laboratory investigation showed the following: red blood cells, 3,610,000; white blood cells, 10,750; hemoglobin, 75 per cent; sedimentation rate, 101 mm. in one hour, 125 mm. in two hours. Urinalysis was essentially negative. Kahn—

negative; Friedman test—negative. The patient ran a low-grade temperature and was treated on admission for an acute upper respiratory infection. This subsided, but the fever persisted and was then ascribed as being due to degenerative changes within the tumor.

On Dec. 21, 1945, a celiotomy was performed through a subumbilical midline incision. An almost solid lobulated mass about the size of a child's head was found in the right lower portion of the abdomen. On its surface was a considerable quantity of grayish-white partially organized fibrous exudate. In the process of delivering the mass from the abdomen a large cystic area was opened allowing a considerable quality of serosanguineous fluid to escape within the abdominal cavity. The tumor was attached to the right broad ligament by a broad thick vascular pedicle. Adhesions existed between the tumor and the pelvic floor. These were freed with blunt dissection without penetrating the capsule. The pedicle was transfixed and ligated, and the tumor removed. The entire pelvic floor was thickened, due, undoubtedly, to organization of inflammatory exudate. The left ovary was not present. Only a small lateral fimbriated portion of a maldeveloped left tube could be demonstrated. In the midline where the uterus would normally be present, one could feel retroperitoneally a thickened mass about 5 cm. in length and of about the diameter of a lead pencil, which probably represented a rudimentary uterus. Further abdominal exploration was unrevealing. The patient's postoperative course was uneventful.

Pathologic Description.—Specimen consisted of an ovarian mass measuring 21 by 14 by 10½ cm. This mass was well encapsulated except for a one-half centimeter in diameter perforation at one end of the tumor from which necrotic material could be expressed. Over the lower end of the tumor the capsule is covered with a grayish-white exudate which represents organized fibrin. The rest of the capsule is smooth and glistening and contains large veins coursing through it. On section, the tumor mass cuts with ease, exposing a large central degenerative cyst measuring 5 cm. in diameter, which is filled with necrotic material, blood clot, and serous fluid. There are numerous areas of cystic degeneration up to 1½ cm. in diameter scattered throughout the tumor. In some places, there is marked hemorrhagic extravasation into the tumor tissue. Between the cystlike areas of degeneration the typical appearance of the tissue is pearly gray, soft, friable, and brainlike. Attached to this ovarian mass is a Fallopian tube which measures 8½ by .8 cm.

Microscopically, sections through various portions of the tumor (Fig. 4) revealed the tissue to be very cellular with scant fibrous tissue interspersed at regular intervals. The cells were arranged in masses, nests, and cords. In some areas there was an attempt at granular formation. The cells were large, round, and polygonal. They had clear cytoplasm with well-demarcated cell margins. The nuclei were large, vesicular, and stained heavily with hematoxylin. Numerous typical and atypical mitotic figures were seen. Sections taken from the periphery of the tumor were very cellular and well preserved. Sections taken closer to the center of the tumor showed large areas of degeneration and necrosis. Other sections showed large areas of hemorrhagic infiltration into the tumor tissue. The capsule showed a marked infiltration of polymorphs, plasma cells, and the laying down of fibrin. There was no infiltration of tumor tissue into the capsule. There was moderate lymphocytic infiltration into the sparse fibrous connective tissue coursing throughout the sections. Diagnosis: Dysgerminoma of the ovary, with marked degenerative changes.

The patient was transferred to a general hospital for deep x-ray therapy. The authors were able to communicate with the patient on April 18, 1946. She had various complaints of an unspecific nature, but nothing to indicate that there had been a recurrence of the tumor.

ADRENAL-LIKE MASCULINIZING TUMOR OF THE OVARY ASSOCIATED WITH BLEEDING FIBROMYOMA UTERI

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(From the Crawford W. Long Memorial Hospital)

THE literature on adrenal-like tumor of the ovary is limited by the paucity of material and is complicated by marked diversity in nomenclature and classification. The tumor is variously called adrenal tumor, adrenal carcinoma, adrenal cortex carcinoma, hypernephroma, hypernephroid tumor, interstitioma, lipoid-cell tumor, and luteoma of the ovary. Rottino and McGrath[1] have coined the etymologically objectionable Latin-Greek hybrid "masculinovoblastoma" which is only clinically descriptive. The masculinization syndrome produced by these tumors must be distinguished from that due to pituitary basophilism or to androgenic tumors arising from the adrenal gland itself instead of the ovary.

Barzilai,[2] in 1943, stated that less than ten cases of what he chose to call "virilizing lipoid cell tumor of the ovary" had been described. He also stated that "one and the same tumor has occasionally been described under different names." Kepler, Dockerty, and Priestly[3] exhaustively reviewed the literature on adrenal tumors of the ovary in 1944, collecting thirteen cases to which they added one of their own. Since then four additional cases have been reported.[4-6] The ages of the patients varied from 15 to 62 years, and all of them had amenorrhea. No mention was made of the coexistence of fibromyoma uteri in any case, but one was associated with bilateral dermoid cysts of the ovary. Hypertension was present in four of six cases, and not mentioned in ten. Obesity was pronounced in eight cases. All patients had masculine hirsutism in some degree, and eleven of thirteen had voice changes. Hypertrophy of the clitoris was present in ten of the twelve cases in which the organ was described.

Glycosuria existed in six of eleven cases in which the urinalysis was noted. Four individuals had definite tendency toward polycythemia vera. Hormone studies were seldom made, but usually showed elevated androgens and diminished gonadotropins and estrogens.

The masculinization syndrome was completely cured in four patients, one of which later had a normal pregnancy. Virilism was improved to some degree in seven other cases. Vaginal bleeding occurred for the first time in sixteen years on the ninth postoperative day of a patient who died two days later. One patient died at operation, and another died of recurrence after four years.

The right ovary was involved in eight cases and the left in seven, while in one case the tumor was bilateral. The tumor varied in size from microscopic dimensions to 15 cm. by 14 cm. by 9 cm. A definite capsule existed in all cases described and ovarian origin of the tumor was identified in all. The cut surface of the tumor was of yellow to orange color in all tumors described, most of which were said to be slightly lobulated.

Case Report

The patient, aged 54 years, white, gravida iii, para iii, was admitted to Crawford W. Long Hospital Jan. 9, 1946, and discharged Jan. 25, 1946. She was 62 inches in height and weighed 200 pounds. Her blood pressure was

180/100. The chief complaint was irregular vaginal bleeding of thirty-six months' duration. There had been no definite amenorrheic phase of the menopause, but she had experienced flushes and sweats occasionally. In June, 1945, she began to grow reddish brown hair on the lips, chin, cheeks, chest, and extremities. Her skin, formerly normal, began to have a flushed appearance, and soon acne of the face, chest, and shoulders occurred. Her voice became husky and she had to give up singing, a definite handicap to her as a leader of church activities. Previously frigid, she began to experience orgasms for the first time in her married life of twenty-six years.

Examination of the head and neck revealed a florid rotund face and the acne described by the patient. The facial lesions were mostly cicatrized. The cheeks, chin, lips, neck, shoulders, and extremities were covered with reddish brown hair of medium texture, which on the exposed surfaces had been altered by bleaches and pumice stone. The breasts were rather small in proportion to the obesity of the patient.

Extreme obesity handicapped the examination of the abdomen. An irregular, firm, painless tumor of indeterminate size occupied the suprapubic region. The clitoris was enlarged to 3.5 by 1.5 cm., and was quite erectile. When erect the distended corpora cavenosa gave the dorsum a grooved appearance. The mucosa of the vestibule and the vagina was definitely atrophic. The cervix showed a few retention cysts, but was otherwise normal except for fixation. The corpus uteri was enlarged to the total bulk of about a ten weeks' pregnancy by two or more discrete nodules. It was mobile without discomfort. The adnexa could not be satisfactorily outlined on account of the obesity of the patient. Blood count was normal. Urinalysis showed trace of albumin and sugar and an occasional hyaline cast.

Impression was (1) fibromyomatous uterus and (2) virilism with acne and hypertension which suggested extragenital origin, possibly pituitary basophilism, etc. It was decided that the patient should have total hysterectomy because of the possible coexistence of adenocarcinoma of the corpus uteri.

Laparotomy was performed Jan. 15, 1946. The uterus was fairly symmetrically enlarged but nodular in consistency. The largest discrete nodule described preoperatively was found to be a solid tumor of the left ovary about 4 cm. by 3 cm. by 4 cm. The capsule was smooth and glistening, through which could be seen lobulated orange-yellow material. The right ovary and both tubes were of normal postmenopausal type. The cervix was fixed by thickened cardinal ligaments. Total hysterectomy and bilateral salpingo-oophorectomy were performed.

Convalescence was normal and rapid and the wound healed primarily. By the eighth day the acne was improving and the hypertension had disappeared, the blood pressure being 130/80. The patient was transferred to her home on the tenth postoperative day.

Pathological Report.—(Dr. Everett L. Bishop). The specimen consisted of a large uterus with the cervix and adnexa. The cervix showed a few small cysts, and the canal was filled with mucus. The uterus was 8 cm. in diameter, the enlargement due to several fibromyomas, one of which was 4.5 cm. in diameter and compressed the uterine mucosa. The endometrium was atrophic, and there was an area of organized hemorrhage where it was compressed by the tumor as described. There were several smaller fibrous tumors scattered throughout the myometrium. The Fallopian tubes were grossly normal. There was one small hydatid cyst.

The right ovary was very sclerotic, measuring 3.5 by 1.5 by 1 cm. The left ovary measured 5 by 5 by 3 cm., had a smooth capsule, and cut surface

showed a solid mass of brilliant, orange colored, moderately firm, but not hard tissue without necrosis or hemorrhage.

Microscopic: Sections of the cervix showed the usual fibromuscular structure with active glands and numerous cysts, some of which were filled with mucus. Sections of the uterus showed a diffuse fibrosis of the muscle. The fibromyomatous tumor showed no degenerative changes. The endometrium was thin and atrophic with intact surface epithelium and a few glands of medium and small size. There was a large area of hemorrhage into the endometrium, but no ulceration. Sections of the small right ovary showed a very dense sclerotic structure without follicles or cysts. Sections of the larger ovary showed only a narrow covering layer of identifiable ovarian tissue in which were numerous congested vessels, several large cells containing dark brown pigment, but no follicles or cysts. The bulk of the mass was composed of a broad sheet of large, faintly granular, lipoid type of cells with very little supporting connecting tissue, but with numerous blood vessels of various sizes. In a few places some of the cells were smaller with more opaque and granular cytoplasm. There was an occasional small area of hemorrhage, but no necrosis. There were no giant cells of any type.

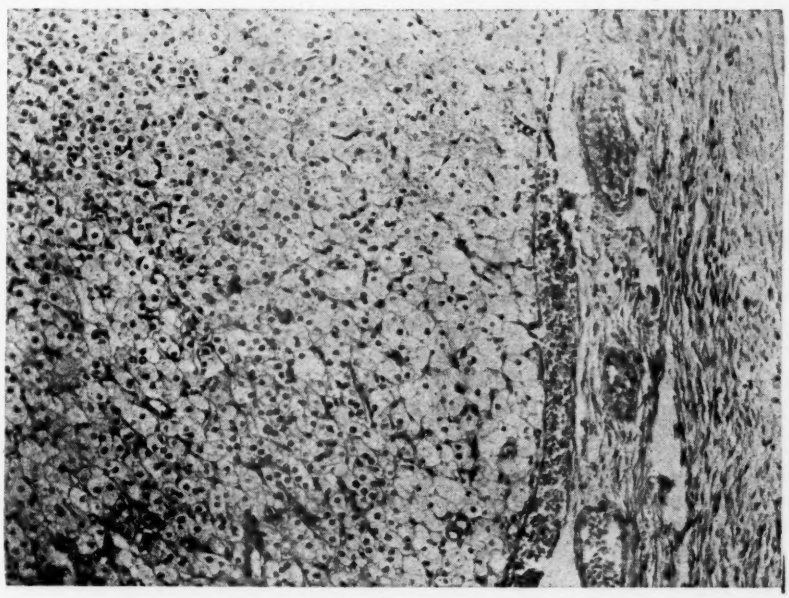

Fig. 1.—Section of tumor and capsule of ovarian tissue.

Pathologic diagnosis: Adrenal tumor of ovary; multiple fibromyoma of the uterus with infarction of atrophic endometrium.

At the follow-up examination twelve weeks after operation, the patient was apparently well. Her weight had decreased to 178 pounds, the blood pressure was 140/83, and the urine was normal. The voice was slightly improved, but the patient still could not risk singing in public. The hirsutism was much improved; the hair on the chest, shoulders, and extremities had largely disappeared, despite the patient not having used a depilatory or pumice stone since the operation. The facial hirsutism was still present but in a markedly lessened degree. The acne had entirely disappeared. The clitoris was slightly smaller.

Summary

A short review of the literature on the adrenal-like tumor of the ovary with masculinization syndrome is given. A case is reported which is the only one in literature which was associated with vaginal bleeding of any kind, this bleeding being due to fibromyoma uteri compressing atrophic endometrium. The tumor was apparently benign, and the patient was markedly improved by operation.

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ABSORPTION OF PENICILLIN FROM THE VAGINA

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WE WISH to report briefly the blood levels and urinary excretion of penicillin following the administration of single large doses by the vaginal route. Available literature contains no information on this method of administering penicillin,[1] yet such information is a necessary preliminary to the use of the drug in the local infections commonly encountered in obstetrics and gynecology.

Ten patients on the Gynecological Service were selected for this study. Seven were normal menstruating women, two had had the menopause, and one had had three months of amenorrhea in consequence of an endocrine disorder associated with virilism. Vaginal and cervical infections and other local lesions were absent in all cases. After a vaginal douche of sterile water, five suppositories of calcium penicillin in a base of cocoa butter were placed in the vagina at one time. Each suppository contained 100,000 units of penicillin. In each case the pH of the vagina was determined before and after treatment by means of the Beckman pH Meter, Laboratory Model. For the determination of penicillin in the blood, a modification of the Rammelkamp method was employed, *Staphylococcus aureus* strain H being used as the test organism. Urinary excretion studies were done for twenty-four hours after treatment.

After the intravaginal administration of 500,000 Oxford units the average penicillin level in the blood was 0.38 units per c.c. of serum at the end of thirty minutes; 1.35 units per c.c. at the end of one hour; 0.96 units per c.c. at the end of two hours; and 0.38 units per c.c. at the end of three hours. Wide individual variations were observed which may in part be due to leakage from the introitus (Fig. 1).

Before treatment, the pH of the vagina varied between 4.1 and 7.0. Five hours after treatment the pH varied between 6.3 and 7.5. In a control series of five women treated with plain cocoa butter suppositories, vaginal pH was unchanged after five hours. The total urinary excretion of penicillin in twenty-four hours varied between 33,425 units and 142,000 units, the average being 91,957 units.

TABLE I. BLOOD LEVELS ATTAINED BY VARIOUS METHODS OF ADMINISTRATION

AUTHOR	ROUTE	DOSAGE (UNITS)	LEVELS AT THE END OF			
			½ HR.	1 HR.	2 HR.	3 HR.
Herrell et al[3]	Intramuscularly	50,000		0.96		0.06
Romansky and Rittman[4]	Intramuscularly (beeswax-peanut oil)	66,400		0.039	0.078	0.078
	Intramuscularly	85,000	0.625	0.31	0.15	0.039
Schwartzman[5]	Intramuscularly	100,000	2-6	0.6-4.0	0.1-2.0	0.04-0.8
Gerber et al[6]	Intramuscularly	100,000	6.6*	2.5	1.0	
	Intramuscularly	200,000	11.4*	4.3	1.2	
	Intramuscularly	300,000	16.0*	9.5	2.3	
This Study	Intravaginal	500,000	0.38	1.35	0.96	0.38

*Twenty minutes.

Comment

It is evident from these observations that penicillin is readily absorbed through the vaginal mucosa and appears in the blood in high therapeutic levels. The method is painless. The suppositories are well tolerated and can be administered by the patients themselves. No untoward local or systemic toxic effects were observed. Absorption from the vagina was found to be somewhat slower and more prolonged than absorption after intramuscular injection (Table I).

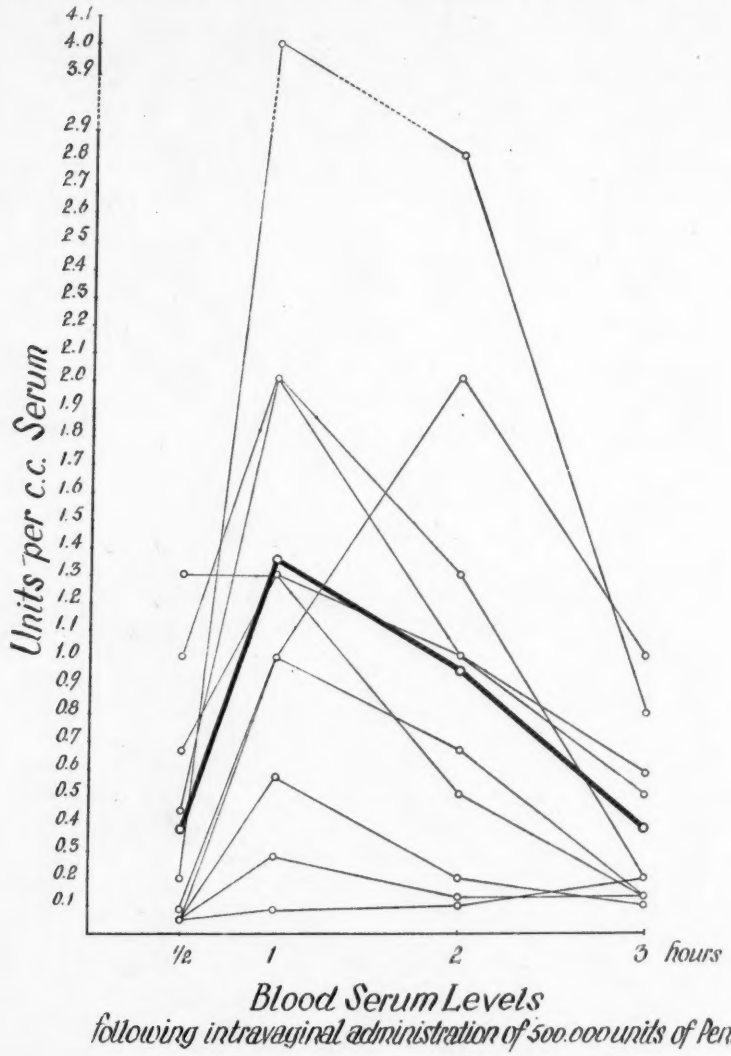

Fig. 1.—Blood levels of penicillin after intravaginal administration of 500,000 units. The heavy line indicates the average.

By the latter method the highest serum levels are achieved in approximately twenty to thirty minutes, whereas after intravaginal administration the maximum is obtained after one hour. Therapeutic levels of penicillin were maintained up to three hours in all cases. It may therefore be possible to use the vagina as a depot from which continuous absorption of penicillin may be achieved. Further studies are in progress to determine the blood levels attained by the use of smaller doses at various intervals.

TABLE II

CASE	AGE (YEARS)	RACE	MENSES	DIAGNOSIS	GRAVIDITY	PRE ℞* pH	5 HR. POST ℞* pH	BLOOD SERUM LEVELS OF PENICILLIN EXPRESSED IN OXFORD UNITS PER C.C. ½ HR.	1 HR.	2 HR.	3 HR.
R. B.	21	Negro	Normal	Fibroid	0	4.7	6.5	0.08	1.0	0.66	0.13
R. K.	50	White	Postmenopause	Fibroid uteri	2	6.5	7.5	0.66	1.3	1.0	0.5
B. S.	42	White	Normal	Cystorectocele	2	4.9	6.3	0.44	2.0	1.0	0.57
R. W.	39	Negro	Normal	Fibroid uteri	3	5.4	6.3	0.55	0.08	0.1	0.2
M. C.	34	Negro	Normal	Fibroid uteri	0	7.0	7.5	0.05	0.27	0.13	0.13
S. F.	39	White	Normal	Fibroid uteri	0	4.1	7.0	1.0	2.0	1.3	0.20
R. Y.	31	White	Amenorrheic	Virilism	4	6.3	7.0	0.05	0.57	0.2	0.1
L. J.	45	Negro	Normal	Fibroid uteri	1	5.6	7.5	0.05	1.0	2.0	1.0
L. K.	31	White	Normal	Ectopic preg.	4	7.0	7.5	1.3	1.3	0.5	0.13
A. R.	49	White	Postmenopause	Fibroid uteri	4	5.0	6.5	0.2	4.0	2.7	0.8

*℞ equals treatment.

TABLE III. URINARY PENICILLIN EXCRETION

3 HOURS		21 HOURS		TOTAL NO. UNITS EXCRETED
VOLUME (C.C.)	UNITS PER C.C.	VOLUME (C.C.)	UNITS PER C.C.	IN 24 HR.
500	200	1,050	1.0	101,050
350	200	800	13	80,400
750	100	1,200	10	87,000
350	50	1,400	27	55,300
600	100	675	4	62,700
150	270	225	13	33,425
280	270	1,400	27	109,400
250	400	1,025	20	120,500
200	400	1,400	27	127,800
325	400	600	20	142,000

Conclusions

1. Penicillin in the form of suppositories is readily absorbed through the vagina.

2. Therapeutic levels are easily attained and maintained for at least three hours.

3. This method warrants clinical trial and may prove to be the method of choice for the administration of penicillin in the adult female.

We wish to express our appreciation to the Schenley Laboratories for the Penicillin used in this study.

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Department of Reviews and Abstracts

Selected Abstracts

Cesarean Section

Perez, Manuel Luis, and Echevarria, Ramon: Prophylactic Sulfonamide-Penicillin Therapy in Unclean Operative Obstetric Cases (Cesarean Section), An. brasil. de ginec. **21:** 339-349, 1946.

The authors have previously shown the beneficial effects of local sulfonamide therapy when performing hysterectomies in unclean cases, as a prophylactic measure against mortality and morbidity. They now report twenty-five cervical cesarean sections, seventeen of which were definitely unclean in which penicillin was used with the sulfonamides. There were no deaths in this series, and the morbidity decreased from the previous incidence of 47.8 per cent to 12 per cent. With few exceptions, 4 Gm. of sulfonamide were implanted intraperitoneally, and 200,000 units of penicillin were given by the intramuscular route. Hence, the addition of penicillin to the sulfonamides were a distinct help. J. P. GREENHILL.

Endocrinology

Weaver, John D.: Estrogenic Hormones, Often Only a Psychotherapeutic Agent, South. M. J. **39:** 581, 1946.

Severe criticism is leveled against the indiscriminate use of the estrogenic hormones. The author has administered peanut oil with and without the estrogenic hormones and obtained equally good results in the relief of symptoms at the climacteric. Use of the estrogens should be restricted to the treatment of gonococcal vulvovaginitis, senile vaginitis, hypoplasia of the uterus, postpartal breast engorgement, some types of habitual abortion, and for its effect upon ovulation.

Circumstantial evidence is presented to indicate that long-continued administration of the estrogens may be carcinogenic. The physician who administers the estrogens without first doing a pelvic examination is sharply criticized. WILLIAM BICKERS.

Endometriosis

Couri, A. A., and Ramos, A. N.: Urogenital Endometriosis, An. brasil de ginec. **11:** 27-33, 1946.

The authors report a case of endometriosis of the bladder which had its origin in the female genitals. In spite of a hysterectomy with removal of the adnexa, the patient's symptoms were not relieved. In fact, they became worse. Examination of the bladder revealed an endometrioma on the anterior wall which had grown inward from the uterine wall. This is the first report of genital endometriosis with bladder involvement reported of genital endometriosis with bladder involvement reported in Brazil. J. P. GREENHILL.

Ectopic Pregnancy

Campos da Paz Fo, A.: Hysterosalpingography in the Diagnosis of Ectopic Pregnancy, Obst. y ginec. latino-am. **3:** 704-712, 1945.

The author is opposed to the use of hysterosalpingography for the diagnosis of tubal pregnancy because he believes the radiologic findings are not characteristic. Analyzing the

findings of several authors who have used the method he emphasizes the variety of x-ray pictures described by them. He criticizes the so-called "lacunar image" which is observed in ectopic pregnancies only exceptionally; however, he presents one such case of his own. He also presents several hysterosalpingograms made to test tubal patency in sterility cases, which show pictures identical to those observed by several authors during tubal abortions, and described as "lacunar images"; in the author's opinion they represent the contrast medium spreading into the peritoneal cavity. Based on this observation, he emphasizes the need for taking several pictures. He establishes a difference between a "permanent picture" and a "transitional picture." In discussing the dangers of the hysterosalpingography in the diagnosis of tubal pregnancy, he reports a case in Dr. A. Sarmento's private practice in which rupture of the tube occurred at the exact moment an exploration was performed.

J. P. GREENHILL.

Weyeneth, R.: Simultaneous Pregnancy in Both Tubes, Monatschr. f. Geburtsh. u. Gynäk. 120: 129-140, 1945.

A case of simultaneous bilateral tubal pregnancy, probably of the same age, is reported by the author. On the right side a rupture of the tube occurred with profuse bleeding into the peritoneal cavity, while on the left side the tubal abortion had taken place with the formation of a tubal hematoma. The etiology was most likely postpartum endometritis and endosalpingitis. This is the seventy-first case of simultaneous bilateral extrauterine pregnancy reported in the literature.

J. P. GREENHILL.

Gynecology

Dionisi, H., and Ferraris, L. V.: Struma Ovarico With Hyperthyroidism, Obst. y ginec. latino-am. 3: 797-811, 1945.

The case of a patient with "struma ovarico," presenting the typical signs of hyperthyroidism and a basal metabolism oscillating between plus 37 and plus 54, is presented. The symptoms disappeared after subtotal thyroidectomy, but manifested themselves again one and one-half years later, when the basal metabolism reached plus 64. The cervix was normal, there were no accessory nor aberrant glands; nevertheless a tumor was discovered in the ovary, the histologic examination of which indicated: struma with marked hyperplasia of the epithelium.

The tumor was removed, and a month later the basal metabolism decreased to plus 8, the signs of hyperthyroidism vanished completely, which plainly shows the relation that existed between the clinical picture and the ovarian struma.

J. P. GREENHILL.

Rieper, J. P.: Comparative Study of Colposcopic and Histologic Findings in Cervical Lesions, An. brasil de ginec. 10: 300-308, 1945.

The author examined twenty women by means of the colposcope and then removed areas of diseased cervical tissue for histologic study. Comparative studies showed that colposcopy permits a correct interpretation of cervical lesions in most instances. In the opinion of the author, biopsy may not correctly explain some cervical lesions. Early carcinoma and atypical epithelial proliferations may readily be recognized by the colposcope, but this instrument is not suitable for advanced cases. Syphilitic and edematous lesions interfere with colposcopic diagnosis. Personal experience with the colposcope is essential for proper utilization of this instrument.

J. P. GREENHILL.

Schockaert, J. A., and Ferin, J.: Endometrial Biopsy as a Diagnostic Aid in Tuberculosis of the Internal Female Genitalia, Uit de Verhandelingen van de Koninklijke Vlaamsche Academie Voor Geneeskunde Van Belgie 4: 5, 1942.

Thanks to the systematic use of endometrial biopsies in gynecologic cases, the authors have been able to discover tuberculosis of the endometrium in more than 2 per cent of their

cases. This frequency was much more than was suspected. Tuberculosis of the endometrium was found in 6 per cent of the sterility cases, even in the absence of all palpable evidence of tubal inflammation. Hence, the authors emphasize that, in so-called essential sterility cases where the menstrual cycle is normal, one must think of tuberculosis.

An endometrial biopsy is indispensable in a gynecologic examination where there is chronic palpable inflammation of the uterine adnexa. The discovery of tuberculosis can readily be made in this way and will lead to early treatment.

The authors insist that every piece of tissue removed by curettage, whether it follows therapy for bleeding for a gynecologic condition or an abortion, be examined routinely. This procedure will permit discovery of tuberculosis in cases where it is not suspected.

J. P. GREENHILL.

De La Osa Garces, Leon Lopez: The Use of Penicillin Solution in Cases of Cervicitis, Toko-Ginecologia Practica 5: 226-239, 1946.

The author applied penicillin locally in cases of cervicitis both in the form of a paste and in the form of a solution. The results were so good that he recommends this form of therapy.

J. P. GREENHILL.

Gynecologic Operations

da Silva Pereira, J. M.: Prolapse of the Female Urethra. Report of Three Cases, Obst. y ginec. latino-am. 3: 848-864, 1945.

Prolapse of the urethra—that is to say hernia of the urethral mucosa through the meatus—is a rare affection which is more frequently observed during childhood and after the menopause.

The author proposes the following classification: first degree prolapse: descent of one of the walls only; second degree prolapse: descent of the distal segment of the urethra; third degree prolapse: descent of both the distal and proximal segments.

The symptomatology is changeable, the most frequent disorders being urinary disturbances, pain, and loss of blood. The principal factors which help to make the diagnosis are analyzed, and the technique of a repair operation is described. The latter consists in: (1) transverse hemisection of the tumor down to the meatus, leaving a mark in every corner of the incision; (2) excision of the upper half and suture of the margins with separate stitches, using thin chromic catgut; (3) excision of the inferior part of the tumor. The last stage is the same as for perineorrhaphies.

The purpose of this intervention is to reduce the orifice of the meatus, in order to prevent recurrence or urinary incontinence.

The prognosis, as a rule, is good, the complications being urethral stenosis and incontinence of urine.

J. P. GREENHILL.

Cirio, C. R.: Myometrectomy. Its Conception, Anatomy, Physiology, Technic, Indications and Results, Obst. y ginec. latino-am. 3: 761-778, 1945.

According to the author, myometrectomy is the most recent technical advance among the menstruation-preserving operations, and the only one that permits the radical extirpation of all the small, invisible, and impalpable nodules situated in the myometrium. Like any other menstruation-preserving technique, it should not be performed after the forty-eighth nor before the fortieth year of life, and if exceptionally it is to be done on women under 40 years it should be reserved for women who have fulfilled their maternal obligations.

The size of the new menstruating organ is that of an infantile uterus and in some cases even smaller, owing to extirpation of the myometrium, that allows a more perfect final peritonization, and consequently a better recovery than other menstruation-preserving operations.

If the mortality caused by myomectomy varies between 1.5 per cent and 3.6 per cent, according to the majority of statistics, the one corresponding to the myometrectomy, according to the author's own statistics, which is the most important one up to the present day, is only 1.4 per cent. J. P. GREENHILL.

Ahumada, Juan C., and Chevalier, Raúl M.: Tubal Surgery and Sterility, Obst. y ginec. latino-am. 4: 71-96, 1946.

The authors review the extensive literature dealing with plastic operations on the Fallopian tubes and implantation of the ovary on the uterine cornu for the purpose of overcoming sterility. They explain in detail and illustrate most of the operations known as salpingostomy, salpingolysis, implantation of the tube, and the Estes operation. They present the indications, the postoperative sequels, the percentages of success as reported in the literature, as well as their own experiences.

The authors have performed 12 surgical interventions. Tubal patency tests were performed on 8 patients and the tubes found open in five cases. Two patients became pregnant; one had an abortion, and one had a normal labor and live baby. J. P. GREENHILL.

Labor, Management, Complications

Monatno, A.: Labor and Sudden Death, Obst. y ginec. latino-am. 3: 945-952, 1945.

There are many conditions that are able to produce sudden death during labor, the most frequent of which possibly is occlusion of the pulmonary artery through emboli or thrombosis. When the clot is large enough to entirely obstruct the artery, the circulation through the whole organism is interrupted, and death occurs nearly instantaneously, without permitting any affection to develop in the lungs. When, on the contrary, the clot is small and only obstructs one of the branches of the artery that supplies a lobule, and especially with stagnation of the blood in the veins (i.e., chronic congestion through heart failure, etc.), an infarct, generally of the hemorrhagic type, appears. This usually does not provoke important disturbances for the patient and disappears in about eight days. Its clinical diagnosis, with the help of some laboratory tests, is as a rule simple, and the most frequent complications are infection of the infarct, repetition, and emboli, which are nearly always fatal.

Treatment of massive emboli is practically impossible. With regard to branch emboli, the indications are: complete rest, oxygen, injections of morphine and papaverine, evacuating enemas, etc. Prophylaxis consists in facilitating the blood flow (by teaching the patient to breathe before and after childbirth), in order to ensure proper ventilation of the lungs.

The most important measure is to avoid infarcts. This consists is modifying the process of blood clotting through the combined use of heparin and dicoumarol, until a prothrombin time of 25 to 30 seconds is attained. Unfortunately, this therapy is not within the possibilities of the general practitioner. J. P. GREENHILL.

Bass, S.: Experiences With Ergobasin Preparations for the Induction of Labor and in the First Stage of Labor, Gynaecologia 121: 3-28, 1946.

This is a report of a method of stimulating labor pains by repeated administration of small doses of quinine, Basergin, and Thymophysin. Special attention is devoted to the effect of Ergobasin. In primary uterine inertia the effect on the whole is good. Great differences occur in the induction of labor according to the indication. In cases of premature rupture of the membranes, the method is practically 100 per cent successful, and in case of prolonged pregnancy failures occur in about one-third. In comparison with the normal, the number of complications in the 437 deliveries was not increased. Ergobasin is harmless if given with care. J. P. GREENHILL.

Sáez, Eduardo Valenzuela: Concerning the Physiopathology of the Cervix and a Modality of Complete Dilatation in Certain Cases of Dystocia of the Lower Pole of the Ovum, Obst. y ginec. latino-am. 4: 280-288, 1946.

The author believes that the character of cervical dilatation is a better criterion for the differentiation between the normal and pathologic courses of labor than are uterine contractions. He reviews the different factors involved in the process of normal delivery, and emphasizes the importance of correct preparation of the birth canal before labor begins. He studied the uterine contractions, the intraovular tension, the cervical musculature, the loosening of the lower pole of the ovum, the bag of waters, and the engagement of the presenting part. He insists upon a peculiar modality in certain cases of dystocia of the lower pole of the ovum when the bag of waters is not properly ballooned out by the engagement of the presenting part. In such cases the dilatation of the cervix is complete, but the cervix has the appearance of a postpartum cervix in that it is totally relaxed. The author believes that the condition is due to lack of engagement and is not inherent in the cervix. Therefore, he believes that the baby should be extracted in such cases. This opinion is borne out by the fact that very few of the babies were born spontaneously. J. P. GREENHILL.

Perez, Manuel Luis, and Baldi, Eduardo M.: The Risks of the Induction of Labor by Aburel's Method, Obst. y ginec. latino-am. 4: 8-19, 1946.

The method of inducing labor adopted by Aburel, namely intra-ovular injection of serum, is popular in South America. The authors encountered three accidents in a series of twenty-five cases. In the first case, the baby showed marks of the needle puncture after delivery; in the second case, the mother died as the result of necrosis of the uterine wall followed by peritonitis, and in the third case the baby developed necrosis of the right leg which resulted in its death.

The authors warn general practitioners against using the Aburel method because, in spite of the advantages of the transabdominal method of inducing labor, a drug which will be harmless for the mother and baby has not yet been discovered. J. P. GREENHILL.

Gosende, Julio C.: Breech Presentation, Bol. Soc. de obst. y ginec. 24: 540-545, 1945.

At the Rosario Maternity Hospital in Buenos Aires from 1930 to 1944, there were 15,298 deliveries. Among them were 386 breech deliveries, an incidence of 4.35 per cent. The total fetal mortality was 21.42 per cent, of which 14.8 per cent were in primiparas, and 6.42 per cent in multiparas. The author emphasizes that breech presentation should be considered under the head of dystocia and not normal labor. In most cases x-ray studies should be made during pregnancy and also during labor. Cesarean section is rarely selected for breech presentation alone, however, when there are additional factors such as contracted pelvis, placenta previa, and advanced age, cesarean section is indicated. J. P. GREENHILL.

Menopause

Barber, H. W.: Dermatoses of the Menopause, Practitioner 156: 333, 1946.

A considerable number and variety of cutaneous changes and of symptoms referable to the skin appear in women near, during, and/or following the menopause, and at an earlier age in those with ovarian hypofunction. Moreover, certain dermatoses, which may occur from childhood to old age, in either sex, may be markedly influenced in their distribution and clinical manifestations, by the menopause. A good deal is known about the pathology of the menopausal and postmenopausal states, but there remains much unknown, particularly regarding the dermatoses. A great deal is known clinically; less, perhaps, therapeutically. However it is a well-established fact that by the judicious use of estrogens many symptoms referable to the skin and associate nervous system are successfully managed. It should be thoroughly understood, however, that estrogen therapy is not a panacea for "all and every"

menopause symptom, for it is a fact that many women do not exhibit strictly menopausal symptoms—and therefore do not need hormone treatment simply because they are passing through or have passed the climacteric, often many years previously.

In conclusion, the author emphasizes that just because a patient is approaching or actually in the midst of the menopause, organotherapy is not necessarily indicated; that the most reliable method of administration is implantation under the skin of estradiol of one of the synthetic estrogens. This method is contraindicated, however, if the patient is still menstruating or has only recently ceased; that hypodermic administration is indicated where rapid and intensified effect is desired; and that oral administration is less satisfactory because of the fact that it is always questionable just how much absorption of the active principle is obtained through this route. Ointments containing a high concentration of synthetic estrogens are now available and, for certain of the dermatoses, this form of therapy may be adequate. HARVEY B. MATTHEWS.

Menstruation, Dysmenorrhea, etc.

Culiner, A.: The Relation of Theca-Cells to Disturbances of the Menstrual Cycle, J. Obst. & Gynaec. Brit. Emp. 52: 545, 1945.

In a previous study it was shown that the baboon, when the theca cells surrounding the ovarian follicles proliferate or luteinize so extensively as to be visible to the naked eye as yellowish plaques or masses, there is often disturbance of the menstrual cycle. There has been much speculation as the endocrine function of the theca cells, especially in relation to theca-cell tumors. The author has made a study of the ovaries and uteri obtained at operation on women with excessive bleeding or other uterine evidence of endocrine disorder. Many of these patients were in the fourth and fifth decades of life, and had previously had normal cycles and pregnancies. Serial sections of the ovaries were examined.

As the ovaries are removed as a rule only for some gynecologic complaint, it is difficult to establish the incidence of theca lutein cells other than those related to corpora lutea in the normal human ovary. In the author's series, luteinized theca-cells were found more frequently than was anticipated, but their extent and distribution was not closely related to the severity of the menstrual disorder. The author proposes the following classification of theca-cell proliferations on the basis of their relation to various types of atresia. Group I, corpus thecale luteum, in which the original form of the follicle is retained; in one subgroup (a) granulosa cells may be absent or degenerating; in another subgroup (b) granulosa cells are luteinized. Group II, corpus thecale luteum fibrosum, in which granulosa cells are not present, absorption of liquor folliculi has taken place, connective tissue cells fill the cavity and may be surrounded by a hyaline ring; luteinized theca cells are external to this ring. Group III, corpus thecale luteum candicans, in which lutein reactions occur around a collapsed corpus atreticum. Group IV, corpus thecale luteum hyalinum, in which there is a lutein reaction around follicles that have collapse with hyaline tissue invading the cavity. Group V, corpus thecale luteum restiforme, in which a lutein reaction occurs around primordial or small maturing follicles. All these types of theca-cell proliferation with luteinization have been observed in the author's material except Group V, which, however, is theoretically possible. In this material a wide range of endometrial reactions and clinical disturbances was observed, but those could not be correlated with the type of theca-cell luteinization observed in the ovary. In a few cases, normal endometria were found, although luteinized theca-cells were present in the ovaries, and there were menstrual disturbances.

From these observations, the author concludes that theca-cell proliferation may occur as part of the process of maturation of the Graafian follicle. Luteinization of theca-cells around atretic follicles may be without clinical significance in ovulatory cycles, but in the presence of extensive thecal luteinization with follicular atresia, disturbances of menstrual rhythm and abnormal bleeding may occur. From the character of the uterine reactions found in association with proliferation of theca-cells, neither estrogenic nor progesteronic action can be definitely attributed to them. It is possible that they are responsible for a third

ovarian hormone that has an androgenic action, or for a modified secretion that disturbs the balance between the hormones acting during the menstrual cycle. The histologic characteristics of some theca-cell tumors of the ovary closely resemble the theca-cell proliferations in atretic follicles. HARVEY B. MATTHEWS.

Gori, Roberto M., Bettinotti, Alberto E., and Bayona, Ernesto: Considerations Concerning the Reactions of Soskin, Wachtel, and Hechter, Obst. y ginec. latino-am. 4: 190-208, 1946.

Modern investigations have shown that the process of menstruation is controlled by the vessels of the endometrium, the changes in which are apparently due to the action of acetylcholine. Therefore, delayed menstruation is now considered to be the result of transient hormonal dysfunction, and in many cases is due to mental, emotional, and other factors. Soskin, Wachtel, and Hechter recommended that these patients be treated with prostigmine, the action of which is similar to that of acetylcholine but without its unpleasant secondary reactions. Prostigmine may also be used for the diagnosis of pregnancy. The authors used prostigmine in 150 women who complained of delayed menstruation. The authors believe that this substance may be safely used to produce bleeding when the delayed menstruation is not due to pregnancy. When bleeding occurs, pregnancy may be ruled out. When bleeding does not occur, further studies must be made. J. P. GREENHILL.

Blanchard, Oscar: Vaginal Smears in the Diagnosis of Ovarian Activity in Women, Obst. y ginec. latino-am. 4: 107-132, 1946.

The author reviews the literature on the subject of cyclic variations in the vaginal mucosa. He points out that the normal vaginal cycle exihibits five principal phases: (1) menstruation, (2) proliferative or follicular phase, (3) intermenstrual period, (4) regressive or secretory phase and (5) premenstrual period. In his study the author used Shorr's method.

In a series of 130 patients, 68 were studied completely for menstrual disturbances. The vaginal smears were taken every other day for a minimal period of forty-five days. In some patients the smears were continued for nearly two years. The author found that vaginal smears proved to be of great help in clarifying menstrual disturbances as well as giving clues to therapeutic action by means of hormones such as estrogens, progesterone, androgens, gonadotrophins, etc.

The author concludes that vaginal smears, like most laboratory studies, are useful diagnostic aids if utilized during complete cycles long enough to eliminate sources of error in their reading and interpretation. However, the vaginal smears must be correlated with or subordinated to the patient's history and the physical examination of the woman.

J. P. GREENHILL.

Correspondence

Vaginal Lacerations Resulting From Coitus

To the Editor:

Since writing a report of three cases of vaginal lacerations resulting from coitus, published in the January issue of the JOURNAL (**53**: 177, 1947), I have encountered another similar case, of special interest because of the patient's age.

CASE 4.—Mrs. M. K., aged 72 years, white, was brought to the hospital at 7:30 P.M. on Nov. 16, 1946, because of profuse vaginal bleeding of two and one-half hours' duration. Her granddaughter stated that the blood had saturated two Turkish towels. The patient offered no information as to the cause of the bleeding. She was faint, her skin was moist and clammy, although her blood pressure was 120/70, her pulse was 80, and of good volume. On pelvic examination, the vulvar and vaginal tissues were found to be elastic and in a good state of preservation for the patient's age, and the introitus admitted two fingers easily. The uterus and adnexa could not be felt. Vaginal bleeding was still profuse, but the cervix remained dry when exposed and sponged. To the right of the cervix, extending through the thickness of the vaginal mucosa, was a fresh laceration, about 3 cm. in length, which was still bleeding. The patient was taken to the operating room, anesthetized with sodium pentothal, and the laceration was repaired. Upon further questioning about the cause of the injury, the patient finally admitted having had voluntary intercourse. Coitus had been painful, and was followed immediately by vaginal bleeding.

The patient is the mother of two children, aged 54 and 53 years. She had a spontaneous menopause thirty years ago, at the age of 42 years, and had not had sexual intercourse for the past sixteen years.

No mention is made of coital trauma as a cause of postmenopausal bleeding in what are perhaps the two most widely quoted papers on the latter subject (Taylor, H. C., Jr., and Millen, R., "The Causes of Vaginal Bleeding and the Histology of the Endometrium After the Menopause," AM. J. OBST. & GYNEC. **36**: 22-39, 1938, a study of 406 cases of postmenopausal bleeding at Roosevelt Hospital between 1921 and 1935; and TeLinde, R. W., "Causes of Postmenopausal Bleeding," *Am. J. Surg.* **48**: 289-293, 1940, a review of all the cases of postmenopausal bleeding seen in the Johns Hopkins Hospital between 1918 and 1935).

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NEW YORK CITY
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Items

The Third American Congress on Obstetrics and Gynecology

The Third American Congress on Obstetrics and Gynecology will be held from September 8 to 12, 1947, in the Municipal Auditorium in St. Louis, Missouri. Dr. Fred L. Adair of Chicago is the General Chairman.

While the Third Congress is similar in scope and program to the two previous meetings, it will be larger in every way. The program under the direction of Dr. William F. Mengert of Dallas is being made up to appeal to the obstetric and gynecologic specialist, to the general practitioner interested in those fields, to the hospital administrator, and to nurses. The program will include sections for the public health doctor and the public health nurse. The medical section of the program is under the direction of Dr. Ralph A. Reis of Chicago as in 1942.

The scientific exhibits are under the guidance of Dr. Jean Paul Pratt of Henry Ford Hospital. The moving picture program is being made up by Dr. John Park of Washington, D. C. Dr. John Rock of Boston heads the committee on evening speakers. The technical exhibit has been arranged by Dr. Philip F. Williams of Philadelphia. A membership committee in every state and in the territories is being set up by Dr. Ralph E. Campbell of Madison, Wisconsin, and plans are under way to have a special committee build up interest in the Congress in Central and South America. Dr. Harvey B. Matthews of Brooklyn heads the committee in charge of publicity. The general advisory committee is in charge of Dr. Howard C. Taylor, Jr. The local organization committee in St. Louis is headed by Dr. Richard Paddock.

The Friday morning sessions of the Congress, September 12, are to be given over entirely to the National Federation of Obstetric-Gynecologic Societies. The program for these sessions will be arranged by a committee working under Dr. James S. Taylor of Altoona. One member of this committee, Dr. E. Lee Dorsett of St. Louis, will arrange an evening speaker for the Federation of nation-wide prominence who will present his viewpoints to a joint meeting of the Congress, the Federation, and the general public. For further information, address Karl S. Richardson, 24 West Ohio Street, Chicago, Ill.

International Congress of Obstetrics and Gynecology
Dublin, Ireland, July 7 to 12, 1947

The program for the Congress includes seven sessions to be devoted on successive days to the following topics: history of midwifery, puerperal sepsis, eclampsia, sterility, fetal and neonatal mortality, and shock in obstetrics. Representative speakers from several countries will discuss these topics, including the British Isles, New Zealand, the United States, Australia, South Africa, Sweden, Palestine, Denmark, Canada, and elsewhere.

Information about travel routes, hotel accommodations, etc., may be obtained from the local offices of Messrs. Thos. Cook and Sons.

American Association of Obstetricians, Gynecologists, and Abdominal Surgeons' Foundation Prize

An annual contest for this award is open to all physicians. Further information may be obtained from the Secretary of the Association, Dr. James R. Bloss, 418 Eleventh Street, Huntington 1, West Virginia.